

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

FEILER, William S.
Morgan & Finnegan, L.L.P.
345 Park Avenue
New York, New York 10154
ETATS-UNIS D'AMERIQUE

PCT

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL PRELIMINARY
EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing
(day/month/year) 19.10.2001

Applicant's or agent's file reference
2026-4302PC

IMPORTANT NOTIFICATION

International application No.
PCT/US00/15446

International filing date (day/month/year)
02/06/2000

Priority date (day/month/year)
04/06/1999

Applicant
THE GOVERNMENT OF THE UNITED STATES OF AMERICA...

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA

European Patent Office P.B. 6818 Patentlaan 2
NL-2280 HV Rijswijk - Pays Bas
Tel. +31 70 340 - 2040 Tx: 31 651 epo nl
Fax: +31 70 340 - 3016

Authorized officer

Cardenas, C

Tel. +31 70 340-33/0





PCT

REC'D 24 OCT 2001

WIPO

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 2026-4302PC	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/US00/15446	International filing date (day/month/year) 02/06/2000	Priority date (day/month/year) 04/06/1999
International Patent Classification (IPC) or national classification and IPC C12N15/51		
Applicant THE GOVERNMENT OF THE UNITED STATES OF AMERICA...		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.



2. This REPORT consists of a total of 8 sheets, including this cover sheet.

- ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☒ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☒ Certain defects in the international application
- VIII ☒ Certain observations on the international application

Date of submission of the demand 02/01/2001	Date of completion of this report 19.10.2001
Name and mailing address of the international preliminary examining authority:  European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized officer Montero Lopez, B Telephone No. +31 70 340 3739 



**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/US00/15446

I. Basis of the report

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

Description, pages:

1-54 as originally filed

Claims, No.:

1-37 as originally filed

Drawings, sheets:

1/21-21/21 as originally filed

Sequence listing part of the description, pages:

1-84, as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☒ contained in the international application in written form.
- ☒ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:



**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/US00/15446

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

- ☐ restricted the claims.
- ☐ paid additional fees.
- ☐ paid additional fees under protest.
- ☒ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

- ☐ complied with.
- ☐ not complied with for the following reasons:

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

- ☐ all parts.
- ☒ the parts relating to claims Nos. 1-11, 33, 34, 37 completely, 12-20, 23, 24, 29-32, 35, 36 partially.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N) Yes: Claims 4-15, 23, 24, 33-37



**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/US00/15446

	No:	Claims	1-3, 16-20, 29-32
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-20, 23, 24, 29-37
Industrial applicability (IA)	Yes:	Claims	1-20, 23, 24, 29-37
	No:	Claims	

2. Citations and explanations
see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet



Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

- D1 : EP-A-0 532 167 {Immuno Japan Inc.}
D2 : Journal of General Virology, 1991, vol. 72, pages 2697-2704,
H. Okamoto et al.
D3 : Nucleic Acids Research, vol. 20, no. 13, April 1991, page 3520,
J.H. Han et al.
D4: Biochemistry, 1998, vol. 37, no. 10, pages 3392-3401, D. L. Sali et al.
D5: Antiviral Research, 1999, vol. 42, pages 59-70, J. Martín et al.

1. The underlying application relates to a nucleic acid molecule which encodes human hepatitis C virus of genotype 2a, DNA constructs comprising said nucleic acid, RNA transcript of said construct, cell transfected with said transcript, hepatitis C virus polypeptide produced by said cell and whose genome comprises said nucleic acid, method for assaying candidate antiviral agents against for activity against HCV using said cell containing HCV, antibody to said polypeptide or to said HCV, method for determining the susceptibility of cells in vitro to support HCV infection using the cells transfected with the nucleic acid of claim 1 and compositions comprising said polypeptide suspended in a pharmaceutically acceptable diluent or excipient.

1.1. D1 discloses a non-A, non-B hepatitis virus RNA, from a strain of NANB called HC-J6 where the genome shares a 96% identity in 9588 base pairs with SEQ ID NO: 1 and a 97.8% identity in 3033 amino acids with SEQ ID NO: 2 of the hepatitis C virus genotype 2a strain HC-J6_{CH} of the present application. D1 also discloses antibodies to the polypeptides of the NANB hepatitis virus.

1.2. D2 discloses the cDNA sequence of the hepatitis C virus isolate HC-J6, also where the genome shares a 96% identity in 9588 base pairs with SEQ ID NO: 1 of the present application.

1.3. D3 discloses the 3' end of the HCV genome which shares a 96% identity in



9588 base pairs with SEQ ID NO: 1 of the present application.

1.4. Consequently, the present application does not satisfy the criterion set forth in Article 33(2) PCT because the subject-matter of claims 1 to 3, 16 to 20 and 29 to 32 is not new in respect of prior art as defined in the regulations (Rule 64(1)-(3) PCT).

2. The subject-matter of claims 4-15, 23, 24, and 33-37 has not been disclosed in the state of the art and therefore claims 4-15, 23, 24 and 33-37 are novel according to Article 33(2) PCT.

2.1. Documents D1 and D2 are considered to represent the most relevant state of the art and disclose the amino and nucleic acid sequences of the HC-J6 strain of hepatitis virus. Due to the fact that the genome sequence of the HC-J6 strain disclosed in D1 and D2 is so closely homologous to the genome sequence of the hepatitis C virus genotype 2a strain HC-J6_{CH} of present application, the person skilled in the art would consider it a matter of routine to produce DNA constructs comprising the nucleic acid of the HC-J6 strain, RNA transcripts comprising said DNA construct or cells transfected with said DNA construct or RNA transcript. The subject-matter of claims 4-15 therefore does not appear to involve an inventive step according to Article 33(3) PCT.

2.2. Claims 23 and 24 involve a method for assaying candidate antiviral agents for activity against HCV comprising exposing a cell containing the HCV of claims 16 or 17 to the candidate antiviral agent. D4 describes the expression of HCV full length NS3 and NS4A in insect cells. The NS3/4A complex was purified and the dependence of the NS3/4A protease activity on buffer conditions, temperature and the presence of detergents was examined. The NS3/4A complex was found to be an attractive target for antiviral therapy against HCV. D5 discloses the effects of amantadine and interferon α -2a on hepatitis C virus markers in cultured peripheral blood mononuclear cells (PBMC). 27% of the patients showed HCV core and NS3 specific proliferative responses. D4 and D5 illustrate the classic methods of assaying candidate antiviral agents for activity against HCV. Consequently the person skilled in the art would consider it a matter of routine to use said methods adapted to the HCV cell from the HCV genotype 2a in a method to assay for



candidate antiviral agents for activity against HCV. The subject-matter of claims 23 and 24 does therefore not satisfy the criterion set forth in Article 33(3) PCT as the subject-matter of said claims does not involve an inventive step (Rule 65(1)(2) PCT).

2.3. Claims 33 and 34 involve a method for determining the susceptibility of cells *in vitro* to support HCV infection. In a similar manner to the testing of an antiviral agent, the person skilled in the art would consider it a matter of routine to determine whether cells *in vitro* are able to support HCV infection. The subject-matter of claims 33 and 34 do not appear to add any inventive features to the claims on which they depend. Claims 33 and 34 are therefore considered not to involve an inventive step according to Article 33(3) PCT.

2.4. Furthermore the simple composition of a polypeptide originating from an HCV genotype 2a and a pharmaceutically acceptable carrier, is also considered to be a matter of routine procedure, obvious to the person skilled in the art and therefore not involving any inventive skill according to Article 33(3) PCT. Claims 35 to 37 are therefore also not inventive according to Article 33(3) PCT.

Re Item VII

Certain defects in the international application

1. Contrary to the requirements of Rule 5.1(a)(ii) PCT, many of the relevant prior art documents are not mentioned in the description.

Re Item VIII

Certain observations on the international application

1. An independent claim must specify clearly all the essential technical features necessary to define the invention. In the present case the nucleic acid and amino acid sequences of the HCV genotype 2a provided by SEQ. ID. NOs: 1 and 2 respectively are considered to be essential technical features which allow the unambiguous characterization of the products concerned. Accordingly the feature of the SEQ. ID.



**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/US00/15446

NOs: 1 and 2 should be present into the independent Claim 1 in order to satisfy the requirements of clarity according to Article 6 and Rule 6(3)(b) PCT.

2. Claims 19 and 20 involve "a polypeptide encoded by the nucleic acid sequence according to...", however claim 21 indicates that only the specific NS3 protease, E1 protein, E2 protein or NS4 proteins are claimed. Due to the fact that nucleic acid sequences of claims 1 and 3 encode different HCV polypeptides, claims 19 and 20 encompass HCV polypeptides other than those in claim 21 and therefore the subject-matter of claims 19 and 20 is vague and unclear and open to interpretation.

3. A product is not rendered novel merely by the fact that it is produced by means of a new process. Furthermore claims for products defined in terms of a process are admissible only if the products as such fulfil the requirements of novelty and inventive step according to Articles 33(2) and (3) PCT. Thus claims 12-15 defining a product in terms of a process are construed as claims to the product per se.



From the INTERNATIONAL SEARCHING AUTHORITY

PCT

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT
OR THE DECLARATION

(PCT Rule 44.1)

To:

Morgan & Finnegan, L.L.P.
Attn. FEILER, William S.
345 Park AvenueNew York, New York 10154 2026-4302 PC
UNITED STATES OF AMERICA ATTY KAMDUE May 23, 2001 (U.S. Suppl IDS Due)1 mo. call-up April 23, 2001BY JMDate of mailing
(day/month/year)

23/02/2001

Applicant's or agent's file reference

2026-4302PC

FOR FURTHER ACTION

See paragraphs 1 and 4 below

International application No.

PCT/US 00/15446

International filing date
(day/month/year)

02/06/2000

Applicant

THE GOVERNMENT OF THE UNITED STATES OF AMERICA...

- 1.
- ☒
- The applicant is hereby notified that the International Search Report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:

The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.**Where?** Directly to the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Fascimile No.: (41-22) 740.14.35CASE 2026-4302 PC ATTY KAMDUE April 23, 2001 (Art. 19 Due)**For more detailed instructions,** see the notes on the accompanying sheet.1 mo. call-up March 23, 2001

- 2.
- ☐
- The applicant is hereby notified that no International Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.


- 3.
- ☐
- With regard to the protest**
- against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

- 4.
- Further action(s):**
- The applicant is reminded of the following:

Shortly after **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90bis.1 and 90bis.3, respectively, before the completion of the technical preparations for international publication.Within **19 months** from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).Within **20 months** from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the International Searching Authority

 European Patent Office, P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl.
Fax: (+31-70) 340-3016

Authorized officer

Catherine Humbert



NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions, respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.



The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

- (i) the claim is unchanged;
- (ii) the claim is cancelled;
- (iii) the claim is new;
- (iv) the claim replaces one or more claims as filed;
- (v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."
2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."
3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."
4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international application is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments and any accompanying statement, under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the time of filing the amendments (and any statement) with the International Bureau, also file with the International Preliminary Examining Authority a copy of such amendments (and of any statement) and, where required, a translation of such amendments for the procedure before that Authority (see Rules 55.3(a) and 62.2, first sentence). For further information, see the Notes to the demand form (PCT/IPEA/401).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.



PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 2026-4302PC	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/US 00/ 15446	International filing date (day/month/year) 02/06/2000	(Earliest) Priority Date (day/month/year) 04/06/1999
Applicant THE GOVERNMENT OF THE UNITED STATES OF AMERICA...		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 11 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

- a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

☒ contained in the international application in written form.

☒ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☐ **Certain claims were found unsearchable** (See Box I).

3. ☒ **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

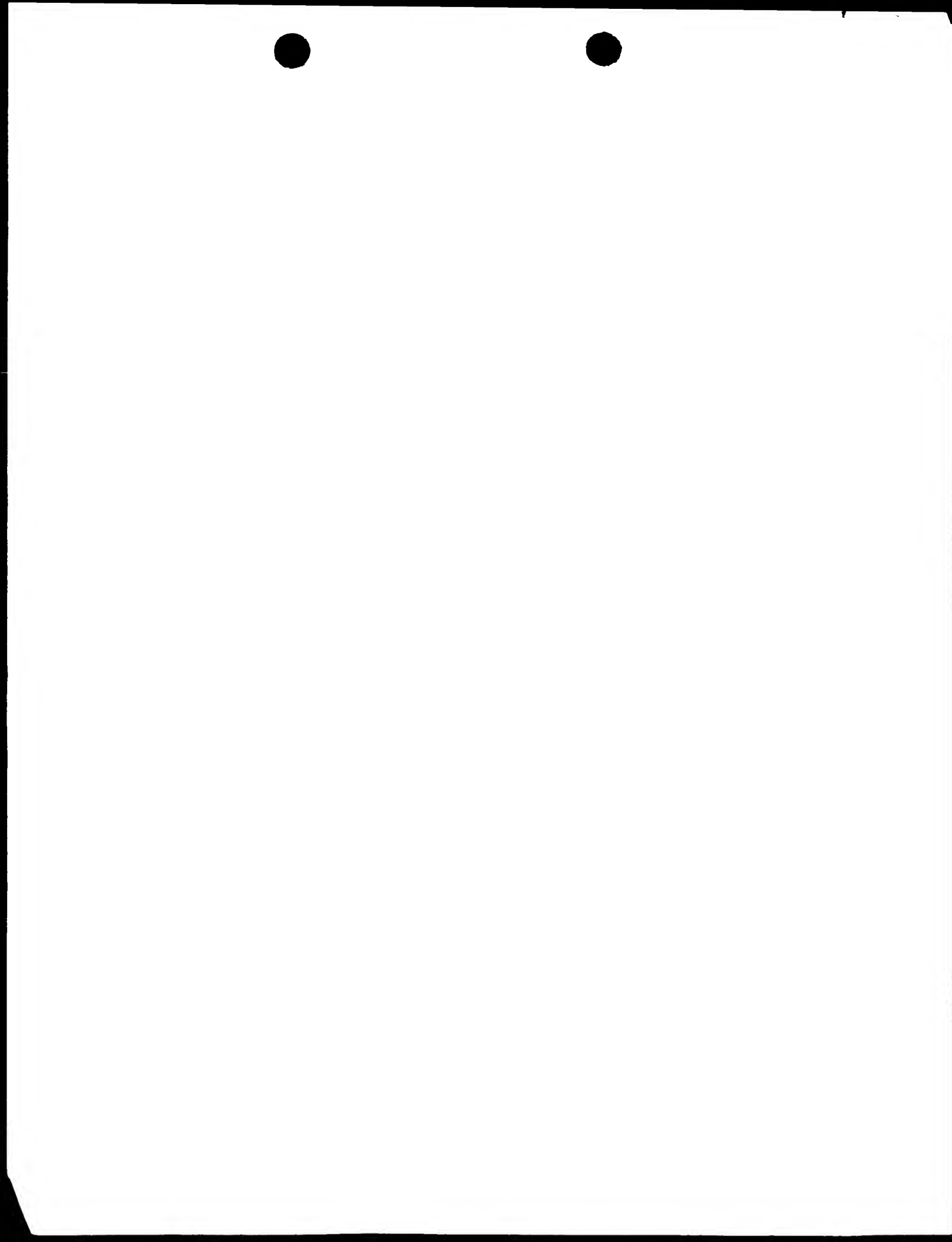
6. The figure of the **drawings** to be published with the abstract is Figure No.

☒ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

1
☐ None of the figures.



INTERNATIONAL SEARCH REPORT

International Application No.

PCT/JP 00/15446

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C12N15/51 C07K14/18 C07K16/18 A61K38/00 A61K39/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07K C12N A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, EMBASE, MEDLINE, STRAND, CAB Data, WPI Data, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 532 167 A (JAPAN IMMUNO INC) 17 March 1993 (1993-03-17) the whole document	1-37
X	H. OKAMOTO ET AL.: "Nucleotide sequence of the genomic RNA of hepatitis C virus isolated from a human carrier: comparison with reported isolates for conserved and divergent regions." JOURNAL OF GENERAL VIROLOGY, vol. 72, 1991, pages 2697-2704, XP000911895 the whole document	1-37

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

° Special categories of cited documents:

A document defining the general state of the art which is not considered to be of particular relevance

E earlier document but published on or after the international filing date

L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

O document referring to an oral disclosure, use, exhibition or other means

P document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

& document member of the same patent family

Date of the actual completion of the international search

6 February 2001

Date of mailing of the international search report

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Hix, R



C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	HAN J H ET AL: "GROUP SPECIFIC SEQUENCES AND CONSERVED SECONDARY STRUCTURE AT THE 3' END OF HCV GENOME AND ITS IMPLICATION FOR VIRAL REPLICATION" NUCLEIC ACIDS RESEARCH, OXFORD UNIVERSITY PRESS, SURREY, GB, vol. 20, no. 13, April 1992 (1992-04), page 3520 XP000938816 ISSN: 0305-1048 the whole document ---	1-3
Y	M. YANAGI ET AL.: "Transcripts of a chimeric cDNA clone of Hepatitis C virus genotype 1b are infectious in vivo." VIROLOGY, vol. 244, 1998, pages 161-172, XP002149625 cited in the application the whole document ---	1-20, 23, 24, 29-37
Y	OHNO T. ET AL: "New hepatitis C virus (HCV) genotyping system that allows for identification of HCV genotypes 1a, 1b, 2a, 2b, 3a, 3b, 4, 5a, and 6a." JOURNAL OF CLINICAL MICROBIOLOGY, (1997) 35/1 (201-207)., XP000911892 the whole document ---	1-20, 23, 24, 29-37
Y	HASHIMOTO M. ET AL: "Typing six major hepatitis C virus genotypes by polymerase chain reaction using primers derived from nucleotide sequences of the NS5 region." INTERNATIONAL HEPATOLOGY COMMUNICATIONS, (1996) 4/5 (263-267)., XP000911896 the whole document ---	1-20, 23, 24, 29-37
Y	YONG YUAN ZHANG ET AL: "Greater diversity of hepatitis C virus genotypes found in Hong Kong than in Mainland China." JOURNAL OF CLINICAL MICROBIOLOGY, (1995) 33/11 (2931-2934)., XP000911893 the whole document ---	1-20, 23, 24, 29-37
Y	FOX S A ET AL: "Rapid genotyping of hepatitis C virus isolates by dideoxy fingerprinting." JOURNAL OF VIROLOGICAL METHODS, (1995 MAY) 53 (1) 1-9., XP000911899 the whole document --- -/--	1-20, 23, 24, 29-37



INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 00/15446

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
P,X	M. YANAGI ET AL.: "Hepatitis C Virus: An infectious molecular clone of a second major genotype (2a) and lack of viability of intertypic 1a and 2a chimeras." VIROLOGY, vol. 262, 1999, pages 250-263, XP000911930 the whole document	1-37
Y	DE FRANCESCO R. ET AL: "A zinc binding site in viral serine proteinases." BIOCHEMISTRY, (1996) 35/41 (13282-13287) , XP000981213 the whole document	12-26, 29-32, 35-37
Y	STEMPNIAK M. ET AL: "The NS3 proteinase domain of hepatitis C virus is a zinc-containing enzyme." JOURNAL OF VIROLOGY, (1997) 71/4 (2881-2886), XP000981212 the whole document	12-26, 29-32, 35-37
Y	Y.M. PARK ET AL.: "Monitoring antibody titers to recombinant core-NS3 fusion polypeptide is useful for evaluating hepatitis C virus infection and responses to interferon-alpha therapy" J. KOREAN MED. SCI., vol. 14, April 1999 (1999-04), pages 165-170, XP000980030 the whole document	12-32, 35-37
Y	L.M. MISON ET AL.: "Prevalence of hepatitis C virus and genotype distribution in an Australian volunteer blood donor population." TRANSFUSION, vol. 37, January 1997 (1997-01), pages 73-78, XP000981247 the whole document	12-26, 29-32, 35-37
P,X	WRIGHT-MINOUE J. ET AL: "Cross-genotypic interaction between hepatitis C virus NS3 protease domains and NS4A cofactors." JOURNAL OF HEPATOLOGY, (2000) 32/3 (497-504). , XP000981249 the whole document	12-26, 29-32, 35-37
A	WO 91 15575 A (CHIRON CORP) 17 October 1991 (1991-10-17) the whole document	12-26, 29-32, 35-37

-/--



C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	MARTIN J. ET AL: "In vitro effect of amantadine and interferon.alpha.- 2a on hepatitis C virus markers in cultured peripheral blood mononuclear cells from hepatitis C virus-infected patients." ANTIVIRAL RESEARCH, (1999) 42/1 (59-70). , XP000980547 the whole document ---	23-28
Y	URUSHIHARA A. ET AL: "Changes in antibody titers to hepatitis C virus following interferon therapy for chronic infection." JOURNAL OF MEDICAL VIROLOGY, (1994) 42/4 (348-356). , XP000980020 the whole document ---	23-28
Y	D.L. SALI ET AL.: "Serine protease of Hepatitis C virus expressed in insect cells as the NS3/4A complex" BIOCHEMISTRY, vol. 37, no. 10, 1998, pages 3392-3401, XP002159433 the whole document ---	25,26
P,X	WO 00 26418 A (UNIV LELAND STANFORD JUNIOR) 11 May 2000 (2000-05-11) the whole document ---	12-24, 27-32, 35-37
X	P.L. CALVO ET AL.: "Hepatitis C virus heteroduplex tracking assay for genotype determination reveals diverging Genotype 2 isolates in Italian hemodialysis patients." JOURNAL OF CLINICAL MICROBIOLOGY, vol. 36, no. 1, January 1998 (1998-01), pages 227-233, XP000981214 the whole document ---	12-24, 29-32, 35-37
X	BUKH J ET AL: "At least 12 genotypes of hepatitis C virus predicted by sequence analysis of the putative E1 gene of isolates collected worldwide." PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA,US,NATIONAL ACADEMY OF SCIENCE. WASHINGTON, vol. 90, September 1994 (1994-09), pages 8234-8238, XP002159434 ISSN: 0027-8424 cited in the application the whole document --- -/--	12-24, 29-32, 35-37



C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
X	P. SIMMONDS ET AL.: "Identification of genotypes of hepatitis C virus by sequence comparisons in the core, E1 and NS-5 regions." JOURNAL OF GENERAL VIROLOGY, vol. 75, 1994, pages 1053-1061, XP000979107 the whole document	12-24, 29-32, 35-37
A	--- L.J. VAN DOORN ET AL.: "Sequence analysis of hepatitis C virus genotypes 1 to 5 reveals multiple novel subtypes in the Benelux countries." JOURNAL OF GENERAL VIROLOGY., vol. 76, 1995, pages 1871-1876, XP000979102 the whole document	12-24, 29-32, 35-37
X	--- WU CHAODONG ET AL.: "Antibody response to E2 glycoprotein induced in mice by immunization with plasmid DNA containing sequence derived from a Chinese genotype III/2a isolate of hepatitis C virus." CHINESE MEDICAL JOURNAL, vol. 112, no. 2, February 1999 (1999-02), pages 166-168, XP000980092 the whole document	12-24, 29-32, 35-37
X	--- N. YUKI ET AL.: "Quantitative analysis of antibody to Hepatitis C virus Envelope 2 Glycoprotein in patients with chronic Hepatitis C virus infection." HEPTOLOGY, vol. 23, no. 5, May 1996 (1996-05), pages 947-952, XP000981263 the whole document	29-32
X	--- G. LONGOMBARDO ET AL.: "Immune response to an epitope of the NS4 protein of Hepatitis C virus in HCV-related disorders." CLINICAL IMMUNOLOGY AND IMMUNOPATHOLOGY, vol. 87, May 1998 (1998-05), pages 124-129, XP000981260 the whole document	12-22, 29-32
X	--- F. FABRIZI ET AL.: "Hepatitis C virus genotypes in chronic dialysis patients." NEPHROL. DIAL. TRANSPLANT., vol. 11, 1996, pages 679-683, XP000981328 the whole document	29-32
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INTERNATIONAL SEARCH REPORT

International Application No.

PC 00/15446

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
X	H-H. LIN ET AL.: "Serotypes, genotypes and levels of Hepatitis C Viremia in pregnant women in Taiwan." J. FORMOS MEDL ASSOC., vol. 95, no. 6, 1996, pages 429-434, XP000981246 the whole document ---	29-32
X	M. DEVESEA ET AL.: "Reduced antibody reactivity to Hepatitis C virus antigen in Hemodialysis patients coinfectd with hepatitis B virus." CLINICAL AND DIAGNOSTIC LABORATORY IMMUNOLOGY, vol. 4, no. 6, November 1997 (1997-11), pages 639-642, XP000981261 the whole document ---	29-32
X	N. YUKI ET AL.: "Hepatitis C virus replicative levels and efficiency of genotyping by specific PCR and antibody assay." JOURNAL OF CLINICAL MICROBIOLOGY, vol. 35, no. 5, May 1997 (1997-05), pages 1184-1189, XP000981255 the whole document ---	29-32
X	Z-X.ZHANG ET AL.: "Evaluation of the multiple peptide assay for typing of antibodies to the Hepatitis C Virus: Relation to genomic typing by the Polymerase Chain Reaction." JOURNAL OF MEDICAL VIROLOGY, vol. 45, 1995, pages 50-55, XP000569306 the whole document ---	29-32
X	H. NOMURA ET AL.: "Interferon therapy and Hepatitis C virus." JOURNAL OF GASTROENTEROLOGY AND HEPATOLOGY, vol. 14, no. 1, January 1999 (1999-01), pages 85-89, XP000980021 the whole document ---	27,28
X	N. FURUSYO ET AL.: "Differences between interferon-alpha and -beta treatment for patients with chronic hepatitis C virus infection." DIGESTIVE DISEASES AND SCIENCES., vol. 44, no. 3, March 1999 (1999-03), pages 608-617, XP000981254 the whole document --- -/--	27,28



PC 00/15446

Form PCT/ISA/210 (continuation of second sheet) (July 1992)



FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-11, 33, 34,
37 completely and partially claims 12-20, 23, 24,
29-32, 35, 36 and 37

A purified and isolated nucleic acid molecule which encodes human hepatitis C virus of genotype 2a, DNA constructs comprising said nucleic acid, RNA transcript of said construct, cell transfected with said transcript, hepatitis C virus polypeptide produced by said cell and whose genome comprises said nucleic acid, method for assaying candidate antiviral agents against for activity against HCV using said cell containing HCV, antibody to said polypeptide or to said HCV, method for determining the susceptibility of cells in vitro to support HCV infection using the cells transfected with the nucleic acid of claim 1 and compositions comprising said polypeptide suspended in a pharmaceutically acceptable diluent or excipient.

2. Claims: 25 and 26 completely and 12-23, 24, 29-32, 35,
36 and 37 partially

A hepatitis C virus polypeptide produced by a cell transfected with a DNA construct comprising a nucleic acid molecule which encodes human hepatitis C virus of genotype 2a which is an NS3 protease and method for assaying candidate antiviral agents against for activity against HCV comprising exposing said HCV protease to candidate antiviral agents, antibody to said polypeptide or HCV and compositions comprising said polypeptide suspended in a pharmaceutically acceptable diluent or excipient.

3. Claims: 12-23, 24, 29-32, 35, 36 and 37 partially

A hepatitis C virus polypeptide produced by a cell transfected with a DNA construct comprising a nucleic acid molecule which encodes human hepatitis C virus of genotype 2a which is an E1 protein, antibody to said polypeptide or HCV and compositions comprising said polypeptide suspended in a pharmaceutically acceptable diluent or excipient..

4. Claims: 12-23, 24, 29-32, 35, 36 and 37 partially

A hepatitis C virus polypeptide produced by a cell transfected with a DNA construct comprising a nucleic acid molecule which encodes human hepatitis C virus of genotype 2a which is an E2 protein, antibody to said polypeptide or HCV and compositions comprising said polypeptide suspended



FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

in a pharmaceutically acceptable diluent or excipient.

5. Claims: 12-23, 24, 29-32, 35, 36 and 37 partially

A hepatitis C virus polypeptide produced by a cell transfected with a DNA construct comprising a nucleic acid molecule which encodes human hepatitis C virus of genotype 2a which is an NS4 protein, antibody to said polypeptide or HCV and compositions comprising said polypeptide suspended in a pharmaceutically acceptable diluent or excipient..

6. Claim : 27 and 28 completely

Antiviral agent identified as having antiviral activity for HCV by the method of claims 23 and/or 25.



INTERNATIONAL SEARCH REPORT

national application No.
PCT/US 00/15446

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☒ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☒ No protest accompanied the payment of additional search fees.



INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No.

PCT/US 00/15446

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0532167 A	17-03-1993	JP 6121689 A	06-05-1994
		JP 6133778 A	17-05-1994
		CA 2075611 A	10-02-1993
		US 5428145 A	27-06-1995
WO 9115575 A	17-10-1991	AU 7675491 A	30-10-1991
		CA 2079105 A	05-10-1991
		EP 0527788 A	24-02-1993
		IE 911129 A	09-10-1991
		PL 169273 B	28-06-1996
		US 5585258 A	17-12-1996
		US 5597691 A	28-01-1997
		US 5371017 A	06-12-1994
		US 5712145 A	27-01-1998
		US 5885799 A	23-03-1999
WO 0026418 A	11-05-2000	AU 1462300 A	22-05-2000



2026-4302 PC
MullerFrom the:
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

FEILER, William S.
Morgan & Finnegan, L.L.P.
345 Park Avenue
New York, New York 10154
ETATS-UNIS D'AMERIQUE

PCT

CASE 2026-4302 PC ATY KAM

DUE August 17, 2001 (with opinion) WRITTEN OPINION

1 mo. call-up July 17, 2001 (PCT Rule 66)

BY J.M.

Date of mailing

(day/month/year)

17.05.2001

Applicant's or agent's file reference

2026-4302PC

REPLY DUE

within 3 month(s)

from the above date of mailing

International application No.

PCT/US00/15446

International filing date (day/month/year)

02/06/2000

Priority date (day/month/year)

04/06/1999

International Patent Classification (IPC) or both national classification and IPC

C12N15/51

Applicant

THE GOVERNMENT OF THE UNITED STATES OF AMERICA...

1. This written opinion is the **first** drawn up by this International Preliminary Examining Authority.

2. This opinion contains indications relating to the following items:

- I ☒ Basis of the opinion
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☒ Lack of unity of invention
- V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain document cited
- VII ☒ Certain defects in the international application
- VIII ☒ Certain observations on the international application

3. The applicant is hereby **invited to reply** to this opinion.

When? See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also: For an additional opportunity to submit amendments, see Rule 66.4.
For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 bis.
For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 04/10/2001.

Name and mailing address of the international preliminary examining authority:

European Patent Office - P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk - Pays Bas
Tel. +31 70 340 - 2040 Tx: 31 651 epo nl
Fax: +31 70 340 - 3016

Authorized officer / Examiner

Hix, R

Formalities officer (incl. extension of time limits)

Sinanovic, E

Telephone No. +31 70 340 2672





I. Basis of the opinion

1. With regard to the **elements** of the international application (Replacement *sheets* which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed"):

Description, pages:

1-54 as originally filed

Claims, No.:

1-37 as originally filed

Drawings, sheets:

1/21-21/21 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:



☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

IV. Lack of unity of invention

1. In response to the invitation (Form PCT/IPEA/405) to restrict or pay additional fees, the applicant has:

- ☐ restricted the claims.
☐ paid additional fees.
☐ paid additional fees under protest.
☒ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with for the following reasons and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees:

3. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this opinion:

- ☐ all parts.
☒ the parts relating to claims Nos. 1-11, 33, 34, 37 completely, 12-20, 23, 24, 29-32, 35, 36 partially.

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement
Novelty (N) Claims 1-3, 16-20, 29-32
Inventive step (IS) Claims 4-15, 23, 24, 33-37
Industrial applicability (IA) Claims

2. Citations and explanations
see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:



see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet



IV. Lack of unity (Continuation)

The IPEA agrees with the ISA that the different subject-matters of the present application are not so linked as to form a single general inventive concept (Rule 13.1 PCT) for the following reasons;

The prior art DI: Journal of General Virology, 1991, vol. 72, pages 2697-2704, H. Okamoto et al. discloses the cDNA sequence of the hepatitis C virus isolate HC-J6.

DII: Journal of Clinical Microbiology, 1997, vol. 35, no. 1, pages 201-207, T. Ohno et al. describes the genotyping of HCV based on PCR of the core region with genotype specific primers for the determination of HCV genotypes 1a, 1b, 2a, 2b, 3a, 3b, 4, 5a and 6a.

DIII: International Hepatology Communications, 1996, vol. 4, pages 263-267, M. Hashimoto et al. discloses a genotyping system using primers from the HS5 region allows determination of the HCV genotypes 1a, 1b, 2a, 2b and 3b

In view of the state of the art the problem may therefore be defined as the provision of the complete nucleic acid sequence which comprises the genome of infectious HCV genotype 2a.

The present application provides the solutions of ;

1.} the complete nucleic acid sequence which comprises the genome of infectious HCV genotype 2a.

2.} a hepatitis C virus polypeptide produced by a cell transfected with a DNA construct comprising a nucleic acid molecule which encodes human hepatitis C virus of genotype 2a which is;

2.1} an NS3 protease,

2.2} an E1 protein,

2.3} an E2 protein,

2.4} an NS4 protein, and

3.} Antiviral agent identified as having antiviral activity for HCV by the method of claims 23 and/or 25.



Consequently due to the fact that the isolate comprising the HCV 2a genotype, DI is known in the state of the art, and that genotyping methods to different coding regions of the HCV genome have been used in the state of the art to identify HCV 2a genotypes due to the fact that the different solutions essentially different in terms of technical structure and function and due to the absence of further technical features which could provide a common novel and inventive linking concept, the IPEA is of the opinion that there is no single inventive concept underlying the set of claimed inventions of the present application according to Rule 13.1 PCT.

There is therefore lack of unity and the different inventions, not belonging to a common inventive concept are formulated as the following different subjects according to Article 17{3}{a} PCT;

Invention 1: Claims 1-11, 33, 34, 37 completely and partially claims 12-20, 23, 24, 29-32, 35, 36 and 37: A purified and isolated nucleic acid molecule which encodes human hepatitis C virus of genotype 2a, DNA constructs comprising said nucleic acid, RNA transcript of said construct, cell transfected with said transcript, hepatitis C virus polypeptide produced by said cell and whose genome comprises said nucleic acid, method for assaying candidate antiviral agents against for activity against HCV using said cell containing HCV, antibody to said polypeptide or to said HCV, method for determining the susceptibility of cells in vitro to support HCV infection using the cells transfected with the nucleic acid of claim 1 and compositions comprising said polypeptide suspended in a pharmaceutically acceptable diluent or excipient.

Invention 2: Claims 25 and 26 completely and 12-23, 24, 29-32, 35, 36 and 37 partially: A hepatitis C virus polypeptide produced by a cell transfected with a DNA construct comprising a nucleic acid molecule which encodes human hepatitis C virus of genotype 2a which is an **NS3 protease** and method for assaying candidate antiviral agents against for activity against HCV comprising exposing said HCV protease to candidate antiviral agents, antibody to said polypeptide or HCV and compositions comprising said polypeptide suspended in a pharmaceutically acceptable diluent or excipient.



Invention 3: Claims 12-23, 24, 29-32, 35, 36 and 37 partially: A hepatitis C virus polypeptide produced by a cell transfected with a DNA construct comprising a nucleic acid molecule which encodes human hepatitis C virus of genotype 2a which is an

E1 protein, antibody to said polypeptide or HCV and compositions comprising said polypeptide suspended in a pharmaceutically acceptable diluent or excipient.

Invention 4: Claims 12-23, 24, 29-32, 35, 36 and 37 partially: A hepatitis C virus polypeptide produced by a cell transfected with a DNA construct comprising a nucleic acid molecule which encodes human hepatitis C virus of genotype 2a which is an

E2 protein, antibody to said polypeptide or HCV and compositions comprising said polypeptide suspended in a pharmaceutically acceptable diluent or excipient.

Invention 5: Claims 12-23, 24, 29-32, 35, 36 and 37 partially: A hepatitis C virus polypeptide produced by a cell transfected with a DNA construct comprising a nucleic acid molecule which encodes human hepatitis C virus of genotype 2a which is an

NS4 protein, antibody to said polypeptide or HCV and compositions comprising said polypeptide suspended in a pharmaceutically acceptable diluent or excipient.

Invention 6: Claims 27 and 28 completely: **Antiviral agent** identified as having antiviral activity for HCV by the method of claims 23 and/or 25.



V. Reasoned statement (Continuation)

Invention 1: Claims 1-11, 33, 34, 37 completely and partially claims 12-20, 23, 24, 29-32, 35, 36 and 37: A purified and isolated nucleic acid molecule which encodes human hepatitis C virus of genotype 2a, DNA constructs comprising said nucleic acid, RNA transcript of said construct, cell transfected with said transcript, hepatitis C virus polypeptide produced by said cell and whose genome comprises said nucleic acid, method for assaying candidate antiviral agents against for activity against HCV using said cell containing HCV, antibody to said polypeptide or to said HCV, method for determining the susceptibility of cells in vitro to support HCV infection using the cells transfected with the nucleic acid of claim 1 and compositions comprising said polypeptide suspended in a pharmaceutically acceptable diluent or excipient.

a. CITATIONS

Reference is made to the following documents:

D1 : EP-A-0 532 167 {Immuno Japan Inc.}

D2 : Journal of General Virology, 1991, vol. 72, pages 2697-2704,
H. Okamoto et al.

D3 : Nucleic Acids Research, vol. 20, no. 13, April 1991, page 3520,
J.H. Han et al.

D4: Biochemistry, 1998, vol. 37, no. 10, pages 3392-3401, D. L. Sali et al.

D5: Antiviral Research, 1999, vol. 42, pages 59-70, J. Martín et al.

b. NOVELTY (Art. 33(2) PCT)

- i. D1 discloses a non-A, non-B hepatitis virus RNA, from a strain of NANB called HC-J6 where the genome shares a 96% identity in 9588 base pairs with SEQ ID NO: 1 and a 97.8% identity in 3033 amino acids with SEQ ID NO: 2 of the hepatitis C virus genotype 2a strain HC-J6_{CH} present application. D1 also discloses antibodies to the polypeptides of the NANB hepatitis virus.



- ii. D2 discloses the cDNA sequence of the hepatitis C virus isolate HC-J6, also where the genome shares a 96% identity in 9588 base pairs with SEQ ID NO: 1 of the present application.
 - iii. D3 discloses the 3' end of the HCV genome which shares a 96% identity in 9588 base pairs with SEQ ID NO: 1 of the present application.
 - iv. The present application does not satisfy the criterion set forth in Article 33(2) PCT because the subject-matter of claims 1 to 3 , 16 to 20 and 29 to 32 is not new in respect of prior art as defined in the regulations (Rule 64(1)-(3) PCT).
- c. INVENTIVE STEP (Art. 33(3) PCT)
- i. Documents D1 and D2 are considered to represent the most relevant state of the art and discloses the amino and nucleic acid sequences of the HC-J6 strain of hepatitis virus.
 - ii. Due to the fact that the genome sequence of the HC-J6 strain disclosed in D1 and D2 is so closely homologous to the genome sequence of the hepatitis C virus genotype 2a strain HC-J6_{CH} present application, the person skilled in the art would consider it a matter of routine to produce DNA constructs comprising the nucleic acid of the HC-J6 strain, RNA transcripts comprising said DNA construct or cells transfected with said DNA construct or RNA transcript.
 - iii. The subject-matter of claims 4 to 15 therefore do not appear to involve an inventive step according to Article 33{3} PCT.
 - iv. Claims 23 and 24 involve a method for assaying candidate antiviral agents for activity against HCV comprising exposing a cell containing the HCV of claims 16 or 17 to the candidate



antiviral agent.

- v. D4 describes the expression of HCV full length NS3 and NS4A in insect cells. The NS3/4A complex was purified and the dependence of the NS3/4A protease activity on buffer conditions, temperature and the presence of detergents was examined. The NS3/4A complex was found to be an attractive target for antiviral therapy against HCV.
- vi. D5 discloses the effects of amantadine and interferon α -2a on hepatitis C virus markers in cultured peripheral blood mononuclear cells (PBMC). 27% of the patients showed HCV core and NS3 specific proliferative responses.
- vii. D4 and D5 illustrate the classic methods of assaying candidate antiviral agents for activity against HCV. Consequently the person skilled in the art would consider it a matter of routine to use said methods adapted to the HCV cell from the HCV genotype 2a in a method to assay for candidate antiviral agents for activity against HCV.
- viii. The subject-matter of claims 23 and 24 does therefore not satisfy the criterion set forth in Article 33(3) PCT as the subject-matter of said claims does not involve an inventive step (Rule 65(1)(2) PCT).
- ix. Claims 33 and 34 involve a method for determining the susceptibility of cells *in vitro* to support HCV infection. In a similar manner to the testing of an antiviral agent, the person skilled in the art would consider it a matter of routine to determine whether cells *in vitro* are able to support HCV infection. The subject-matter of claims 33 and 34 do not appear to add any inventive features to the claims on which they depend.



- x. Claims 33 and 34 are therefore considered not to involve an inventive step according to Article 33{3} PCT.
- xi. Furthermore the simple composition of a polypeptide originating from an HCV genotype 2a and a pharmaceutically acceptable carrier, is also considered to be a matter of routine procedure, obvious to the person skilled in the art and therefore not involving any inventive skill according to Article 33{3} PCT. Claims 35 to 37 are therefore also not inventive according to Article 33{3} PCT.

VII. Certain defects (Continuation)

- 1. Contrary to the requirements of Rule 5.1(a)(ii) PCT, many of the relevant prior art documents are not mentioned in the description.
- 2. If amendments are filed, it should be by way of replacement pages in the manner stipulated by Rule 66.8(a) PCT. In particular, fair copies of the amendments should be filed preferably in triplicate. Moreover, the applicant's attention is drawn to the fact that, as a consequence of Rule 66.8(a) PCT the examiner is not permitted to carry out any amendments under the PCT procedure, however minor these may be.
- 3. In order to facilitate the examination of the conformity of the amended application with the requirements of Article 34(2)(b) PCT, the applicant is requested to clearly identify the amendments carried out, no matter whether they concern amendments by addition, replacement or deletion, and to indicate the passages of the application as filed on which these amendments are based (see also Rule 66.8(a) PCT). If the applicant regards it as appropriate these indications could be submitted in handwritten form on a copy of the relevant parts of the application as filed.



4. The applicant is requested to note that in accordance with Rule 66.4 (a) PCT the issuance of an additional Written Opinion (WO) is facultative. Moreover, as the final action in the PCT procedure is an International **Preliminary** Examination Report (IPER) and not a decision, a violation of the right to be heard cannot exist. The applicant can not therefore rely on obtaining a second WO before the IPER is issued and is requested to answer this first WO in a complete manner.

VIII. Certain Observations (Continuation)

- 1 The application does not meet the requirements of Article 6 PCT because claims are not clear for the following reasons:
 - 1.1 An independent claim must specify clearly all the essential technical features necessary to define the invention. In the present case the nucleic acid and amino acid sequences of the HCV genotype 2a provided by SEQ. ID. NOs: 1 and 2 respectively are considered to be essential technical features which allow the unambiguous characterization of the products concerned. Accordingly the feature of the SEQ. ID. NOs: 1 and 2 must be incorporated into the independent Claim 1 in order to satisfy the requirements of clarity according to Article 6 and Rule 6{3}{b} PCT.
 - 1.2 Claims 19 and 20 involve "a polypeptide encoded by the nucleic acid sequence according to...", however claim 21 indicates that only the specific NS3 protease, E1 protein, E2 protein or NS4 proteins are claimed. Due to the fact that nucleic acid sequences of claims 1 and 3 encode different HCV polypeptides, claims 19 and 20 encompass HCV polypeptides other than those in claim 21 and therefore the subject-matter of claims 19 and 20 is vague and unclear and open to interpretation.



- 2 A product is not rendered novel merely by the fact that it is produced by means of a new process. Furthermore claims for products defined in terms of a process are admissible only if the products as such fulfil the requirements of novelty and inventive step according to Articles 33{2} and {3} PCT. Thus claims 12 to 15 defining a product in terms of a process are construed as claims to the product per se.



2026-43021
HC

PCT

From the INTERNATIONAL BUREAU

NOTIFICATION OF RECEIPT OF
RECORD COPY

(PCT Rule 24.2(a))

To:

FEILER, William, S.
Morgan & Finnegan, L.L.P.
345 Park Avenue
New York, NY 10154
ETATS-UNIS D'AMERIQUE

Date of mailing (day/month/year) 14 July 2000 (14.07.00)	IMPORTANT NOTIFICATION
Applicant's or agent's file reference 2026-4302PC	International application No. PCT/US00/15446

The applicant is hereby notified that the International Bureau has received the record copy of the international application as detailed below.

Name(s) of the applicant(s) and State(s) for which they are applicants:

THE GOVERNMENT OF THE UNITED STATES OF AMERICA as represented by THE SECRETARY,
DEPARTMENT OF HEALTH AND HUMAN SERVICES (for all designated States except US)
YANAGI, Masayuki et al (for US)

International filing date : 02 June 2000 (02.06.00)

Priority date(s) claimed : 04 June 1999 (04.06.99)

Date of receipt of the record copy
by the International Bureau : 03 July 2000 (03.07.00)

List of designated Offices :

AP : GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW

EA : AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

EP : AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE

OA : BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

National : AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES,
FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD,
MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ,
VN, YU, ZA, ZW

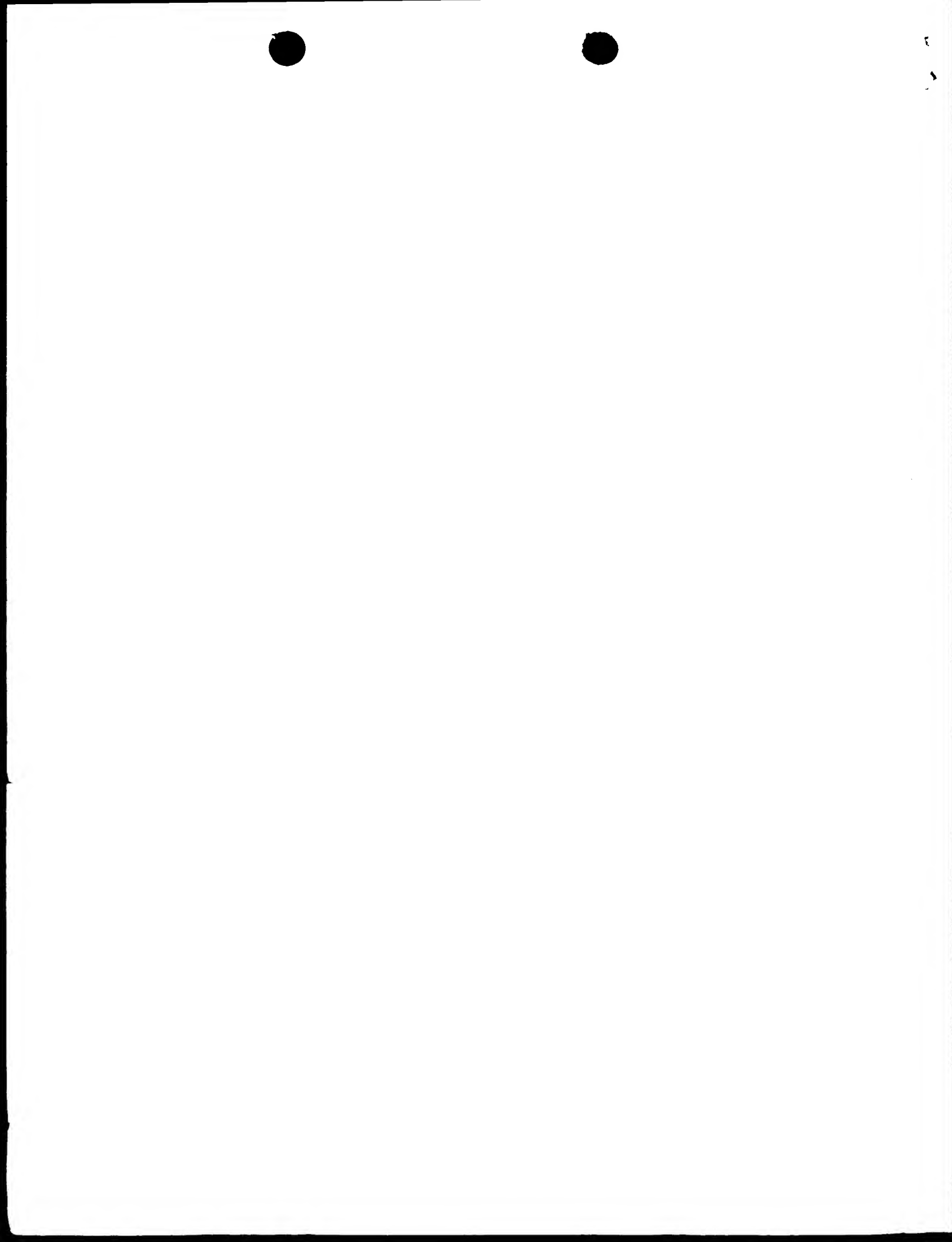
The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Authorized officer:

Peggy Steunenberg

Facsimile No. (41-22) 740.14.35

Telephone No. (41-22) 338.83.38



Continuation of Form PCT/IB/301

NOTIFICATION OF RECEIPT OF RECORD COPY

Date of mailing (day/month/year) 14 July 2000 (14.07.00)	IMPORTANT NOTIFICATION
Applicant's or agent's file reference 2026-4302PC	International application No. PCT/US00/15446

ATTENTION

The applicant should carefully check the data appearing in this Notification. In case of any discrepancy between these data and the indications in the international application, the applicant should immediately inform the International Bureau.

In addition, the applicant's attention is drawn to the information contained in the Annex, relating to:

- ☒ time limits for entry into the national phase
- ☐ confirmation of precautionary designations
- ☒ requirements regarding priority documents

A copy of this Notification is being sent to the receiving Office and to the International Searching Authority.



INFORMATION ON TIME LIMITS FOR ENTERING THE NATIONAL PHASE

The applicant is reminded that the "national phase" must be entered before each of the designated Offices indicated in the Notification of Receipt of Record Copy (Form PCT/IB/301) by paying national fees and furnishing translations, as prescribed by the applicable national laws.

The time limit for performing these procedural acts is **20 MONTHS** from the priority date or, for those designated States which the applicant elects in a demand for international preliminary examination or in a later election, **30 MONTHS** from the priority date, provided that the election is made before the expiration of 19 months from the priority date. Some designated (or elected) Offices have fixed time limits which expire even later than 20 or 30 months from the priority date. In other Offices an extension of time or grace period, in some cases upon payment of an additional fee, is available.

In addition to these procedural acts, the applicant may also have to comply with other special requirements applicable in certain Offices. **It is the applicant's responsibility** to ensure that the necessary steps to enter the national phase are taken in a timely fashion. Most designated Offices do not issue reminders to applicants in connection with the entry into the national phase.

For detailed information about the procedural acts to be performed to enter the national phase before each designated Office, the applicable time limits and possible extensions of time or grace periods, and any other requirements, see the relevant Chapters of Volume II of the PCT Applicant's Guide. Information about the requirements for filing a demand for international preliminary examination is set out in Chapter IX of Volume I of the PCT Applicant's Guide.

GR and ES became bound by PCT Chapter II on 7 September 1996 and 6 September 1997, respectively, and may, therefore, be elected in a demand or a later election filed on or after 7 September 1996 and 6 September 1997, respectively, regardless of the filing date of the international application. (See second paragraph above.)

Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination.

CONFIRMATION OF PRECAUTIONARY DESIGNATIONS

This notification lists only specific designations made under Rule 4.9(a) in the request. It is important to check that these designations are correct. Errors in designations can be corrected where precautionary designations have been made under Rule 4.9(b). The applicant is hereby reminded that any precautionary designations may be confirmed according to Rule 4.9(c) before the expiration of 15 months from the priority date. If it is not confirmed, it will automatically be regarded as withdrawn by the applicant. There will be no reminder and no invitation. Confirmation of a designation consists of the filing of a notice specifying the designated State concerned (with an indication of the kind of protection or treatment desired) and the payment of the designation and confirmation fees. Confirmation must reach the receiving Office within the 15-month time limit.

REQUIREMENTS REGARDING PRIORITY DOCUMENTS

For applicants who have not yet complied with the requirements regarding priority documents, the following is recalled.

Where the priority of an earlier national, regional or international application is claimed, the applicant must submit a copy of the said earlier application, certified by the authority with which it was filed ("the priority document") to the receiving Office (which will transmit it to the International Bureau) or directly to the International Bureau, before the expiration of 16 months from the priority date, provided that any such priority document may still be submitted to the International Bureau before that date of international publication of the international application, in which case that document will be considered to have been received by the International Bureau on the last day of the 16-month time limit (Rule 17.1(a)).

Where the priority document is issued by the receiving Office, the applicant may, instead of submitting the priority document, request the receiving Office to prepare and transmit the priority document to the International Bureau. Such request must be made before the expiration of the 16-month time limit and may be subjected by the receiving Office to the payment of a fee (Rule 17.1(b)).

If the priority document concerned is not submitted to the International Bureau or if the request to the receiving Office to prepare and transmit the priority document has not been made (and the corresponding fee, if any, paid) within the applicable time limit indicated under the preceding paragraphs, any designated State may disregard the priority claim, provided that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity to furnish the priority document within a time limit which is reasonable under the circumstances.

Where several priorities are claimed, the priority date to be considered for the purposes of computing the 16-month time limit is the filing date of the earliest application whose priority is claimed.



PATENT COOPERATION TREATY

2026-4302 PC
K. Moller

From the INTERNATIONAL BUREAU

PCT

INFORMATION CONCERNING ELECTED
OFFICES NOTIFIED OF THEIR ELECTION

(PCT Rule 61.3)

To:

FEILER, William, S.
Morgan & Finnegan, L.L.P.
345 Park Avenue
New York, NY 10154
ETATS-UNIS D'AMERIQUE

Date of mailing (day/month/year) 26 January 2001 (26.01.01)		
Applicant's or agent's file reference 2026-4302PC		IMPORTANT INFORMATION
International application No. PCT/US00/15446	International filing date (day/month/year) 02 June 2000 (02.06.00)	Priority date (day/month/year) 04 June 1999 (04.06.99)
Applicant THE GOVERNMENT OF THE UNITED STATES OF AMERICA as represented by THE SECRETARY, DEPARTMENT OF HEALTH et al		

1. The applicant is hereby informed that the International Bureau has, according to Article 31(7), notified each of the following Offices of its election:

AP : GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW
 EP : AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE
 National : AU, BG, CA, CN, CZ, DE, IL, JP, KP, KR, MN, NO, NZ, PL, RO, RU, SE, SK, US

2. The following Offices have waived the requirement for the notification of their election; the notification will be sent to them by the International Bureau only upon their request:

EA : AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
 OA : BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
 National : AE, AG, AL, AM, AT, AZ, BA, BB, BR, BY, CH, CR, CU, DK, DM, DZ, EE, ES, FI, GB, GD,
 GE, GH, GM, HR, HU, ID, IN, IS, KE, KG, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MW, MX,
 MZ, PT, SD, SG, SI, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW

3. The applicant is reminded that he must enter the "national phase" before the expiration of 30 months from the priority date before each of the Offices listed above. This must be done by paying the national fee(s) and furnishing, if prescribed, a translation of the international application (Article 39(1)(a)), as well as, where applicable, by furnishing a translation of any annexes of the international preliminary examination report (Article 36(3)(b) and Rule 74.1).

Some offices have fixed time limits expiring later than the above-mentioned time limit. For detailed information about the applicable time limits and the acts to be performed upon entry into the national phase before a particular Office, see Volume II of the PCT Applicant's Guide.

The entry into the European regional phase is postponed until 31 months from the priority date for all States designated for the purposes of obtaining a European patent.

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer: Olivia TEFY
Facsimile No. (41-22) 740.14.35	Telephone No. (41-22) 338.83.38



F INTERNATIONAL COOPERATION TREATY

2026-4302 PC

KAM-

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION CONCERNING
SUBMISSION OR TRANSMITTAL
OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

To:

FEILER, William, S.
Morgan & Finnegan, L.L.P.
345 Park Avenue
New York, NY 10154
ETATS-UNIS D'AMERIQUE

Date of mailing (day/month/year) 24 August 2000 (24.08.00)	IMPORTANT NOTIFICATION
Applicant's or agent's file reference 2026-4302PC ✓	
International application No. PCT/US00/15446 ✓	
International publication date (day/month/year) Not yet published	
International filing date (day/month/year) 02 June 2000 (02.06.00) ✓	
Priority date (day/month/year) 04 June 1999 (04.06.99) ✓	
Applicant THE GOVERNMENT OF THE UNITED STATES OF AMERICA as represented by THE SECRETARY, DEPARTMENT OF HEALTH et al	

- The applicant is hereby notified of the date of receipt (except where the letters "NR" appear in the right-hand column) by the International Bureau of the priority document(s) relating to the earlier application(s) indicated below. Unless otherwise indicated by an asterisk appearing next to a date of receipt, or by the letters "NR", in the right-hand column, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).
- This updates and replaces any previously issued notification concerning submission or transmittal of priority documents.
- An asterisk(*) appearing next to a date of receipt, in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b). In such a case, **the attention of the applicant is directed** to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.
- The letters "NR" appearing in the right-hand column denote a priority document which was not received by the International Bureau or which the applicant did not request the receiving Office to prepare and transmit to the International Bureau, as provided by Rule 17.1(a) or (b), respectively. In such a case, **the attention of the applicant is directed** to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

<u>Priority date</u>	<u>Priority application No.</u>	<u>Country or regional Office or PCT receiving Office</u>	<u>Date of receipt of priority document</u>
04 June 1999 (04.06.99) ✓	60/137,693 ✓	US	17 July 2000 (17.07.00)

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. (41-22) 740.14.35	Authorized officer A. Karkachi Telephone No. (41-22) 338.83.38
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PATENT COOPERATION TREATY

26-4302 PC

PCT

NOTICE INFORMING THE APPLICANT OF THE
COMMUNICATION OF THE INTERNATIONAL
APPLICATION TO THE DESIGNATED OFFICES

(PCT Rule 47.1(c), first sentence)

From the INTERNATIONAL BUREAU *Mv/125*

To:

FEILER, William, S.
Morgan & Finnegan, L.L.P.
345 Park Avenue
New York, NY 10154
ETATS-UNIS D'AMERIQUE
MORGAN & FINNEGAN LLP
DEC 28 A 0:44

Date of mailing (day/month/year) 14 December 2000 (14.12.00)		IMPORTANT NOTICE	
Applicant's or agent's file reference 2026-4302PC			
International application No. PCT/US00/15446	International filing date (day/month/year) 02 June 2000 (02.06.00)	Priority date (day/month/year) 04 June 1999 (04.06.99)	
Applicant THE GOVERNMENT OF THE UNITED STATES OF AMERICA as represented by THE SECRETARY, DEPARTMENT OF HEALTH et al			

1. Notice is hereby given that the International Bureau has communicated, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this Notice:
AG,AU,DZ,KP,KR,MZ,US

In accordance with Rule 47.1(c), third sentence, those Offices will accept the present Notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

2. The following designated Offices have waived the requirement for such a communication at this time:

AE,AL,AM,AP,AT,AZ,BA,BB,BG,BR,BY,CA,CH,CN,CR,CU,CZ,DE,DK,DM,EA,EE,EP,ES,FI,GB,GD,
GE,GH,GM,HR,HU,ID,IL,IN,IS,JP,KE,KG,KZ,LC,LK,LR,LS,LT,LU,LV,MA,MD,MG,MK,MN,MW,MX,
NO,NZ,OA,PL,PT,RO,RU,SD,SE,SG,SI,SK,SL,TJ,TM,TR,TT,TZ,UA,UG,UZ,VN,YU,ZA,ZW

The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-bis)).

3. Enclosed with this Notice is a copy of the international application as published by the International Bureau on
14 December 2000 (14.12.00) under No. WO 00/75338

REMINDER REGARDING CHAPTER II (Article 31(2)(a) and Rule 54.2)

If the applicant wishes to postpone entry into the national phase until 30 months (or later in some Offices) from the priority date, a demand for international preliminary examination must be filed with the competent International Preliminary Examining Authority before the expiration of 19 months from the priority date.

It is the applicant's sole responsibility to monitor the 19-month time limit.

Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination.

REMINDER REGARDING ENTRY INTO THE NATIONAL PHASE (Article 22 or 39(1))

If the applicant wishes to proceed with the international application in the national phase, he must, within 20 months or 30 months, or later in some Offices, perform the acts referred to therein before each designated or elected Office.

For further important information on the time limits and acts to be performed for entering the national phase, see the Annex to Form PCT/IB/301 (Notification of Receipt of Record Copy) and Volume II of the PCT Applicant's Guide.

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer J. Zahra
Facsimile No. (41-22) 740.14.35	Telephone No. (41-22) 338.83.38



PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

International Application No.

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference
(if desired) (12 characters maximum) 2026-4302PC

Box No. I TITLE OF INVENTION

CLONED GENOME OF INFECTIOUS HEPATITIS C VIRUS OF GENOTYPE 2a AND USES THEREOF.

Box No. II APPLICANT

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

The Government of the United States of America
as represented by the Secretary, Department of
Health and Human Services
Office of Technology Transfer
National Institutes of Health
6011 Executive Boulevard, Suite 325
Rockville, Maryland 20852
US

☐ This person is also inventor.

Telephone No.
(301) 496-7056

Facsimile No.
(301) 402-0220

Teleprinter No.

State (that is, country) of nationality: US

State (that is, country) of residence: US

This person is applicant for the purposes of: ☐ all designated States ☒ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

YANAGI, Masayuki
257 Congressional Lane, #402
Rockville, Maryland 20852
US

This person is:

☐ applicant only

☒ applicant and inventor

☐ inventor only (If this check-box is marked, do not fill in below.)

State (that is, country) of nationality: JP

State (that is, country) of residence: US

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

☒ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: ☒ agent ☐ common representative

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

FEILER, William S.; BORK, Richard W. and CHEN, Haiyan
Morgan & Finnegan, L.L.P.
345 Park Avenue
New York, New York 10154
US

Telephone No.
(212) 758-4800

Facsimile No.
(212) 751-6849

Teleprinter No.

☐ Address for correspondence: Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.



1

Continuation of Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

If none of the following sub-boxes is used, this sheet should not be included in the request

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

BUKH, Jens
2018 Baltimore Road #J42
Rockville, Maryland 20851
US

This person is:

- ☐ applicant only
☒ applicant and inventor
☐ inventor only (If this check-box is marked, do not fill in below.)

State (that is, country) of nationality:

DK

State (that is, country) of residence:

US

This person is applicant for the purposes of:

- ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

EMERSON, Suzanne U.
4517 Everett Street
Kensington, Maryland 20895
US

This person is:

- ☐ applicant only
☒ applicant and inventor
☐ inventor only (If this check-box is marked, do not fill in below.)

State (that is, country) of nationality:

US

State (that is, country) of residence:

US

This person is applicant for the purposes of:

- ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

PURCELL, Robert H.
17517 White Ground Road
Boyd's, Maryland 20841
US

This person is:

- ☐ applicant only
☒ applicant and inventor
☐ inventor only (If this check-box is marked, do not fill in below.)

State (that is, country) of nationality:

US

State (that is, country) of residence:

US

This person is applicant for the purposes of:

- ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

This person is:

- ☐ applicant only
☐ applicant and inventor
☐ inventor only (If this check-box is marked, do not fill in below.)

State (that is, country) of nationality:

State (that is, country) of residence:

This person is applicant for the purposes of:

- ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

☐ Further applicants and/or (further) inventors are indicated on another continuation sheet.



Box No.V DESIGNATION OF STATES

The following designations are hereby made under Rule 4.9(a) (mark the applicable check-boxes; at least one must be marked):

Regional Patent

- ☒ **AP ARIPO Patent:** GH Ghana, GM Gambia, KE Kenya, LS Lesotho, MW Malawi, SD Sudan, SL Sierra Leone, SZ Swaziland, TZ United Republic of Tanzania, UG Uganda, ZW Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT
- ☒ **EA Eurasian Patent:** AM Armenia, AZ Azerbaijan, BY Belarus, KG Kyrgyzstan, KZ Kazakhstan, MD Republic of Moldova, RU Russian Federation, TJ Tajikistan, TM Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT
- ☒ **EP European Patent:** AT Austria, BE Belgium, CH and LI Switzerland and Liechtenstein, CY Cyprus, DE Germany, DK Denmark, ES Spain, FI Finland, FR France, GB United Kingdom, GR Greece, IE Ireland, IT Italy, LU Luxembourg, MC Monaco, NL Netherlands, PT Portugal, SE Sweden, and any other State which is a Contracting State of the European Patent Convention and of the PCT
- ☒ **OA OAPI Patent:** BF Burkina Faso, BJ Benin, CF Central African Republic, CG Congo, CI Côte d'Ivoire, CM Cameroon, GA Gabon, GN Guinea, GW Guinea-Bissau, ML Mali, MR Mauritania, NE Niger, SN Senegal, TD Chad, TG Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT (if other kind of protection or treatment desired, specify on dotted line)

National Patent (if other kind of protection or treatment desired, specify on dotted line):

- | | |
|---|--|
| <input checked="" type="checkbox"/> AE United Arab Emirates | <input checked="" type="checkbox"/> LR Liberia |
| <input checked="" type="checkbox"/> AL Albania | <input checked="" type="checkbox"/> LS Lesotho |
| <input checked="" type="checkbox"/> AM Armenia | <input checked="" type="checkbox"/> LT Lithuania |
| <input checked="" type="checkbox"/> AT Austria | <input checked="" type="checkbox"/> LU Luxembourg |
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| <input checked="" type="checkbox"/> KR Republic of Korea | Check-boxes reserved for designating States which have become party to the PCT after issuance of this sheet: |
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Precautionary Designation Statement: In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. (Confirmation (including fees) must reach the receiving Office within the 15-month time limit)




Box No. VI PRIORITY CLAIM		<input type="checkbox"/> Further priority claims are indicated in the Supplemental Box.		
Filing date of earlier application (day/month/year)	Number of earlier application	Where earlier application is:		
		national application: country	regional application: regional Office	international application: receiving Office
item (1) 04 June 1999 (04.06.99)	60/137,693	US		
item (2)				
item (3)				

☒ The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) (only if the earlier application was filed with the Office which for the purposes of the present international application is the receiving Office) identified above as item(s): (1)

* Where the earlier application is an ARIPO application, it is mandatory to indicate in the Supplemental Box at least one country party to the Paris Convention for the Protection of Industrial Property for which that earlier application was filed (Rule 4.10(b)(ii)). See Supplemental Box.

Box No. VII INTERNATIONAL SEARCHING AUTHORITY			
Choice of International Searching Authority (ISA) (if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used): ISA / EP	Request to use results of earlier search; reference to that search (if an earlier search has been carried out by or requested from the International Searching Authority): Date (day/month/year) Number Country (or regional Office)		

Box No. VIII CHECK LIST; LANGUAGE OF FILING	
This international application contains the following number of sheets: request : 5 description (excluding sequence listing part) : 54 claims : 5 abstract : 1 drawings : 21 sequence listing part of description : 84 Total number of sheets : 170	This international application is accompanied by the item(s) marked below: 1. <input checked="" type="checkbox"/> fee calculation sheet 2. <input checked="" type="checkbox"/> separate signed power of attorney (Unsigned) 3. <input checked="" type="checkbox"/> copy of general power of attorney; reference number, if any: 4. <input type="checkbox"/> statement explaining lack of signature 5. <input type="checkbox"/> priority document(s) identified in Box No. VI as item(s): 6. <input type="checkbox"/> translation of international application into (language): 7. <input type="checkbox"/> separate indications concerning deposited microorganism or other biological material 8. <input checked="" type="checkbox"/> nucleotide and/or amino acid sequence listing in computer readable form 9. <input checked="" type="checkbox"/> other (specify): Statement under 37 CFR §1.821(f) and WIPO Standard ST. 25; Transmittal Letter
Figure of the drawings which should accompany the abstract: Fig. 1	Language of filing of the international application: English

Box No. IX SIGNATURE OF APPLICANT OR AGENT	
Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request). <div style="text-align: center;">  William S. Feiler Agent for Applicants </div>	

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1. Date of actual receipt of the purported international application: 3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application: 4. Date of timely receipt of the required corrections under PCT Article 11(2): 5. International Searching Authority (if two or more are competent): ISA /	2. Drawings: <input type="checkbox"/> received: <input type="checkbox"/> not received: 6. <input type="checkbox"/> Transmittal of search copy delayed until search fee is paid.

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Continuation of Box No. V - Designation of States

US United States of America - Continuation of US Provisional Application
Serial No. 60/137,693, filed 04 June 1999
(04.06.99)



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FEE CALCULATION SHEET Annex to the Request

For receiving Office use only

International application No.

Date stamp of the receiving Office

Applicant's or agent's
file reference 2026-4302PC

Applicant

The Government of the United States of America as represented by the Secretary, Department of Health and Human Services, et al.

CALCULATION OF PRESCRIBED FEES

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2. SEARCH FEE \$ 990.00 S

International search to be carried out by EP
(If two or more International Searching Authorities are competent in relation to the international application, indicate the name of the Authority which is chosen to carry out the international search.)

3. INTERNATIONAL FEE

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first 30 sheets \$ 427.00 b1

140 x \$10.00 = \$1,400.00 b2

remaining sheets additional amount

Add amounts entered at b1 and b2 and enter total at B \$1,827.00 B

Designation Fees

The international application contains 85 designations.

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1

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
14 December 2000 (14.12.2000)

PCT

(10) International Publication Number
WO 00/75338 A3

(51) International Patent Classification: **C12N 15/51**,
C07K 14/18, 16/18, A61K 38/00, 39/00

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(21) International Application Number: PCT/US00/15446

(22) International Filing Date: 2 June 2000 (02.06.2000)

(74) Agents: **FEILER, William, S.** et al.: Morgan & Finnegan,
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(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/137,693 4 June 1999 (04.06.1999) US

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE,
DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU,
ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS,
LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO,
NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR,
TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(63) Related by continuation (CON) or continuation-in-part
(CIP) to earlier application:
US 60/137,693 (CON)
Filed on 4 June 1999 (04.06.1999)

(84) Designated States (*regional*): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian
patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European
patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE,
IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG,
CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

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Published:
with international search report

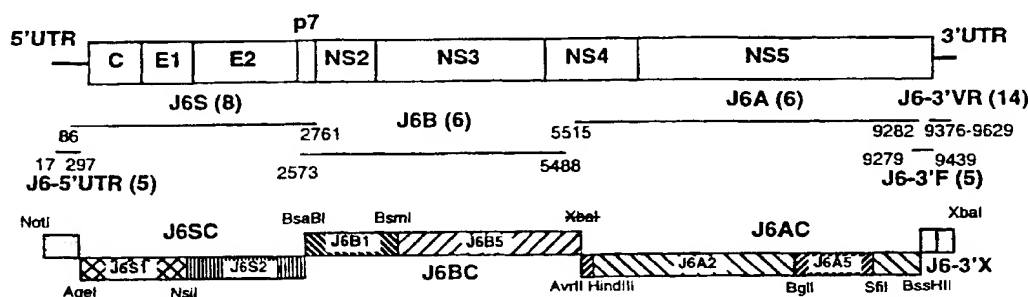
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(88) Date of publication of the international search report:
1 November 2001

*For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.*

(54) Title: CLONED GENOME OF INFECTIOUS HEPATITIS C VIRUS OF GENOTYPE 2a AND USES THEREOF



(57) Abstract: The present invention discloses nucleic acid sequence which encodes infectious hepatitis C virus of strain HC-J6_{CH}, genotype 2a, and the use of the sequence, and polypeptides encoded by all or part of the sequence, in the development of vaccines and diagnostics for HCV and in the development of screening assays for the identification of antiviral agents for HCV.

WO 00/75338 A3



(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
14 December 2000 (14.12.2000)

PCT

(10) International Publication Number
WO 00/75338 A2

(51) International Patent Classification⁷: C12N 15/51,
C07K 14/18, 16/18, A61K 38/00, 39/00

(21) International Application Number: PCT/US00/15446

(22) International Filing Date: 2 June 2000 (02.06.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/137,693 4 June 1999 (04.06.1999) US

(63) Related by continuation (CON) or continuation-in-part (CIP) to earlier application:
US 60/137,693 (CON)
Filed on 4 June 1999 (04.06.1999)

(71) Applicant (for all designated States except US): THE GOVERNMENT OF THE UNITED STATES OF AMERICA as represented by THE SECRETARY, DEPARTMENT OF HEALTH AND HUMAN SERVICES [US/US]; Office of Technology Transfer, National Institutes of Health, Suite 325, 6011 Executive Boulevard, Rockville, MD 20852 (US).

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20852 (US). BUKH, Jens [DK/US]; 2018 Baltimore Road #142, Rockville, MD 20851 (US). EMERSON, Suzanne, U. [US/US]; 4517 Everett Street, Kensington, MD 20895 (US). PURCELL, Robert, H. [US/US]; 17517 White Ground Road, Boyds, MD 20841 (US).

(74) Agents: FEILER, William, S. et al.; Morgan & Finnegan, L.L.P., 345 Park Avenue, New York, NY 10154 (US).

(81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

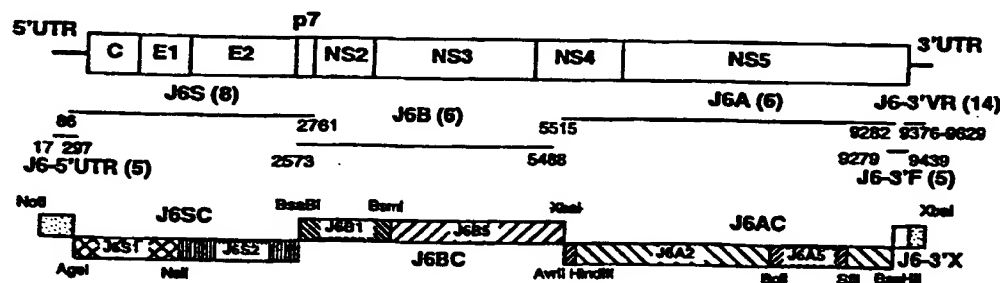
(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:

— Without international search report and to be republished upon receipt of that report.

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: CLONED GENOME OF INFECTIOUS HEPATITIS C VIRUS OF GENOTYPE 2a AND USES THEREOF



(57) Abstract: The present invention discloses nucleic acid sequence which encodes infectious hepatitis C virus of strain HC-J6_{CH}, genotype 2a, and the use of the sequence, and polypeptides encoded by all or part of the sequence, in the development of vaccines and diagnostics for HCV and in the development of screening assays for the identification of antiviral agents for HCV.

WO 00/75338 A2



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Title Of Invention

Cloned Genome Of Infectious
Hepatitis C Virus of Genotype 2a And Uses Thereof

Field Of Invention

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The present invention relates to molecular approaches to the production of nucleic acid sequence which comprises the genome of infectious hepatitis C virus. In particular, the invention provides a nucleic acid sequence which comprises the genome of an infectious hepatitis C virus of genotype 2a. The invention therefore relates to the use of the nucleic acid sequence and polypeptides encoded by all or part of the sequence in the development of vaccines and diagnostic assays for HCV and in the development of screening assays for the identification of antiviral agents for HCV.

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Background Of Invention

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Hepatitis C virus (HCV) has a positive-sense single-strand RNA genome and is a member of the genus *Hepacivirus* within the *Flaviviridae* family of viruses (Rice, 1996). As for all positive-stranded RNA viruses, the genome of HCV functions as mRNA from which all viral proteins necessary for propagation are translated.

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The viral genome of HCV is approximately 9600 nucleotides (nts) in length and consists of a highly conserved 5' untranslated region (UTR), a single long open reading frame (ORF) of approximately 9,000 nts and a complex 3' UTR. The 5' UTR contains an internal ribosomal entry site (Tsukiyama-Kohara et al., 1992;

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- 2 -

Honda et al., 1996). The 3' UTR consists of a short variable region, a polypyrimidine tract of variable length and, at the 3' end, a highly conserved region of approximately 100 nucleotides (Kolykhalov et al., 1996; Tanaka et al., 1995; Tanaka et al., 1996; Yamada et al., 1996). The last 46 nucleotides of this conserved region were predicted to form a stable stem-loop structure thought to be critical for viral replication (Blight and Rice, 1997; Ito and Lai, 1997; Tsuchihara et al., 1997). The ORF encodes a large polypeptide precursor that is cleaved into at least 10 proteins by host and viral proteinases (Rice, 1996). The predicted envelope proteins contain several conserved N-linked glycosylation sites and cysteine residues (Okamoto et al., 1992a). The NS3 gene encodes a serine protease and an RNA helicase and the NS5B gene encodes an RNA-dependent RNA polymerase.

A remarkable characteristic of HCV is its genetic heterogeneity, which is manifested throughout the genome (Bukh et al., 1995). The most heterogeneous regions of the genome are found in the envelope genes, in particular the hypervariable region 1 (HVR1) at the N-terminus of E2 (Hijikata et al., 1991; Weiner et al., 1991). HCV circulates as a quasispecies of closely related genomes in an infected individual. Globally, six major HCV genotypes (genotypes 1-6) and multiple subtypes (a, b, c, etc.) have been identified (Bukh et al., 1993; Simmonds et al., 1993).

The nucleotide and deduced amino acid sequences among isolates within a quasispecies generally differ by < 2%, whereas those between isolates of different genotypes vary by as much as 35%. Genotypes

- 3 -

1, 2 and 3 are found worldwide and constitute more than 90% of the HCV infections in North and South America, Europe, Russia, China, Japan and Australia (Forns and Bukh, 1998). Throughout these regions genotype 1 accounts for the majority of HCV infections but genotypes 2 and 3 each account for 5-15%.

At present, more than 80% of individuals infected with HCV become chronically infected and these chronically infected individuals have a relatively high risk of developing chronic hepatitis, liver cirrhosis and hepatocellular carcinoma (Hoofnagle, 1997). The only effective therapy for chronic hepatitis C, interferon (IFN), alone or in combination with ribavirin, induces a sustained response in less than 50% of treated patients (Davis et al., 1998; McHutchinson et al., 1998). Consequently, HCV is currently the most common cause of end stage liver failure and the reason for about 30% of liver transplants performed in the U.S. (Hoofnagle, 1997). In addition, a number of recent studies suggested that the severity of liver disease and the outcome of therapy may be genotype-dependent (reviewed in Bukh et al., 1997). In particular, these studies suggested that infection with HCV genotype 1b was associated with more severe liver disease (Brecht, 1997) and a poorer response to IFN therapy (Fried and Hoofnagle, 1995). As a result of the inability to develop a universally effective therapy against HCV infection, it is estimated that there are still more than 25,000 new infections yearly in the U.S. (Alter 1997) Moreover, since there is no vaccine for HCV, HCV remains a serious public health problem.

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Despite the intense interest in the development of vaccines and therapies for HCV, progress has been hindered by the absence of a useful cell culture system and the lack of any small animal model for laboratory study. For example, while replication of HCV in several cell lines has been reported, such observations have turned out not to be highly reproducible. In addition, the chimpanzee is the only animal model, other than man, for this disease. Consequently, HCV has been studied only by using clinical materials obtained from patients or experimentally infected chimpanzees, an animal model whose availability is very limited.

However, several researchers have recently reported the construction of infectious cDNA clones of HCV, the identification of which would permit a more effective search for susceptible cell lines and facilitate molecular analysis of the viral genes and their function. For example, Yoo et al., and Dash et al., (1997) (1995) reported that RNA transcripts from cDNA clones of HCV-1 (genotype 1a) and HCV-N (genotype 1b), respectively, resulted in viral replication after transfection into human hepatoma cell lines. Unfortunately, the viability of these clones was not tested in vivo and concerns were raised about the infectivity of these cDNA clones in vitro (Fausto, 1997). In addition, both clones did not contain the terminal 98 conserved nucleotides at the very 3' end of the UTR.

Kolykhalov et al., (1997) and Yanagi et al. (1997, 1998) reported the derivation from HCV strains H77 (genotype 1a) and HC-J4 (genotype 1b) of cDNA clones

- 5 -

° of HCV that are infectious for chimpanzees. However, while these infectious clones will aid in studying HCV replication and pathogenesis and will provide an important tool for development of in vitro replication and propagation systems, it is important to have infectious clones of more than one genotype, given the extensive genetic heterogeneity of HCV and the potential impact of such heterogeneity on the development of effective therapies and vaccines for HCV.

10 In addition, synthetic chimeric viruses can be used to map the functional regions of viruses with different phenotypes. In flaviviruses and pestiviruses, infectious chimeric viruses have been successfully engineered to express different functional units of related viruses (Bray and Lai, 1991; Pletnev et al., 15 1992, 1998; Vassilev et al., 1997) and in some cases it has been possible to make chimeras between non-related or distantly related viruses. For instance, the IRES 20 element of poliovirus or bovine viral diarrhea virus has been replaced with IRES sequences from HCV (Frolov et al., 1998; Lu and Wimmer, 1996; Zhao et al., 1999). Recently, the construction of an infectious chimera of 25 two closely related HCV subtypes has been reported. The chimera contained the complete ORF of a genotype 1b strain but had the 5' and 3' termini of a genotype 1a strain (Yanagi et al., 1998).

30 It is important to determine whether chimeras constructed from more divergent HCV strains are infectious because such chimeras could be used to define the functions of viral units and to dissect the immune response.

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- 6 -

Summary Of The Invention

The present invention relates to nucleic acid sequence which comprises the genome of infectious hepatitis C virus and in particular, nucleic acid sequence which comprises the genome of infectious hepatitis C virus of genotype 2a. It is therefore an object of the invention to provide nucleic acid sequence which encodes infectious hepatitis C virus. Such nucleic acid sequence is referred to throughout the application as "infectious nucleic acid sequence".

For the purposes of this application, nucleic acid sequence refers to RNA, DNA, cDNA or any variant thereof capable of directing host organism synthesis of a hepatitis C virus polypeptide. It is understood that nucleic acid sequence encompasses nucleic acid sequences, which due to degeneracy, encode the same polypeptide sequence as the nucleic acid sequences described herein.

The invention also relates to the use of the infectious nucleic acid sequences to produce chimeric genomes consisting of portions of the open reading frames of nucleic acid sequences of other genotypes (including, but not limited to, genotypes 1, 2, 3, 4, 5 and 6) and subtypes (including, but not limited to, subtypes 1a, 1b, 2a, 2b, 2c, 3a, 4a-4f, 5a and 6a) of HCV. For example, infectious nucleic acid sequence of the 2a strain HC-J6, described herein can be used to produce chimeras with sequences from the genomes of other strains of HCV from different genotypes or subtypes. Nucleic acid sequences which comprise sequences from two or more HCV genotypes or subtypes are designated "chimeric nucleic acid sequences".

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The invention further relates to mutations of the infectious nucleic acid sequence of the invention where mutation includes, but is not limited to, point mutations, deletions and insertions. In one embodiment, a gene or fragment thereof can be deleted to determine the effect of the deleted gene or genes on the properties of the encoded virus such as its virulence and its ability to replicate. In an alternative embodiment, a mutation may be introduced into the infectious nucleic acid sequences to examine the effect of the mutation on the properties of the virus.

The invention also relates to the introduction of mutations or deletions into the infectious nucleic acid sequence in order to produce an attenuated hepatitis C virus suitable for vaccine development.

The invention further relates to the use of the infectious nucleic acid sequence to produce attenuated viruses via passage in vitro or in vivo of the viruses produced by transfection of a host cell with the infectious nucleic acid sequence.

The present invention also relates to the use of the nucleic acid sequence of the invention or fragments thereof in the production of polypeptides where "nucleic acid sequence of the invention" refers to infectious nucleic acid sequence, mutations of infectious nucleic acid sequence, chimeric nucleic acid sequence and sequences which comprise the genome of attenuated viruses produced from the infectious nucleic acid sequence of the invention. In one embodiment, said polypeptide or polypeptides are fully or partially purified from hepatitis C virus produced by cells transfected with nucleic acid sequence of the invention.

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° In another embodiment, the polypeptide or polypeptides are produced recombinantly from a fragment of the nucleic acid sequences of the invention. In yet another embodiment, the polypeptides are chemically synthesized.

5 The polypeptides of the invention, especially structural polypeptides, can serve as immunogens in the development of vaccines or as antigens in the development of diagnostic assays for detecting the presence of HCV in biological samples.

10 The invention therefore also relates to vaccines for use in immunizing mammals especially humans against hepatitis C. In one embodiment, the vaccine comprises one or more polypeptides made from the nucleic acid sequence of the invention or fragment thereof. In
15 a second embodiment, the vaccine comprises a hepatitis C virus produced by transfection of host cells with the nucleic acid sequences of the invention.

20 The present invention therefore relates to methods for preventing hepatitis C in a mammal. In one embodiment the method comprises administering to a mammal a polypeptide or polypeptides encoded by the nucleic acid sequence of the invention in an amount
25 effective to induce protective immunity to hepatitis C. In another embodiment, the method of prevention comprises administering to a mammal a hepatitis C virus of the invention in an amount effective to induce
30 protective immunity against hepatitis C.

35 In yet another embodiment, the method of protection comprises administering to a mammal the nucleic acid sequence of the invention or a fragment thereof in an amount effective to induce protective immunity against hepatitis C.

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The invention also relates to hepatitis C viruses produced by host cells transfected with the nucleic acid sequence of the present invention.

The invention therefore also provides pharmaceutical compositions comprising the nucleic acid sequence of the invention and/or the encoded hepatitis C viruses. The invention further provides pharmaceutical compositions comprising polypeptides encoded by the nucleic acid sequence of the invention or fragments thereof. The pharmaceutical compositions of the invention may be used prophylactically or therapeutically.

The invention also relates to antibodies to the hepatitis C virus of the invention or their encoded polypeptides and to pharmaceutical compositions comprising these antibodies.

The invention also relates to the use of the nucleic acid sequences of the invention to identify cell lines capable of supporting the replication of HCV in vitro.

The invention further relates to the use of the nucleic acid sequences of the invention or their encoded viral enzymes (e.g. NS3 serine protease, NS3 helicase, NS5B RNA polymerase) to develop screening assays to identify antiviral agents for HCV.

Brief Description Of Figures

Figure 1 shows the amplification and cloning of hepatitis C virus genotype 2a (strain HC-J6_{CH}). The nucleotide positions correspond to the sequence of PJ6CF, a full length cDNA clone of hepatitis C virus, genotype 2a, strain HC-J6_{CH}. Products from polymerase

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chain reaction are also shown. The names of the clones obtained from these products are indicated (number of clones sequenced are shown in parenthesis). The composition of the full-length cDNA clone is shown at the bottom. The restriction enzymes used for cloning are indicated. An *Xba*I site in HC-J6_{CH} was eliminated by a silent substitution at position 5494.

Figure 2 shows tree analysis of clones amplified from an infectious acute phase plasma pool generated in a chimpanzee inoculated with human plasma containing strain HC-J6 (Okamoto et al., 1991) as well as a tree of the predicted polyprotein sequence of HC-J6_{CH} and the infectious HC-J6_{CH} cDNA clone (pJ6CF). The nucleotide positions with deletions or insertions were stripped in the analysis of the clones. Multiple sequence alignments and tree analyses were performed with GeneWorks (Oxford Molecular Group) (Bukh et al., 1995). Genotype designations are indicated. Other sequences included in the analysis are HC-J8 (Okamoto et al., 1992), genotype 1a infectious clone BEBE1 (Nakao et al., 1996), H77C (Yanagi et al., 1997); genotype 1b infectious clone J4L6S (Yanagi et al., 1998). The scale in each tree indicates the calculated genetic distance.

Figure 3 shows the alignment of the hypervariable region 1 sequences from 8 J6S clones of strain HC-J6_{CH}. HC-J6_{CH} represents the consensus amino acid sequence of the infectious plasma pool from an experimentally infected chimpanzee. HC-J6 is the published amino acid sequence of the original inoculum (Okamoto et al., 1991).

Figure 4 shows the construction of four intertypic chimeric cDNA clones. White boxes are

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sequences derived from genotype 2a clone pJ6CF, and
black boxes are sequences derived from genotype 1a clone
pCV-H77C (Yanagi et al., 1997). An *NdeI* site (mutation
at position 9158 of pCV-H77C) was eliminated and an
artificial *NdeI* site (mutation at position 2765 of
pCV-H77C) was created by site-directed mutagenesis;
silent mutations are underlined.

Figures 5A and 5B show the alignment of the
nucleotide sequences of the 5' (Fig. 5A) and 3' UTRs
(Fig. 5B) and the amino acid sequences of E2/p7/NS2
junctions (Fig. 5B) in the intertypic 1a, 2a chimeric
cDNA clones. In the 5' UTR alignment, the first 39 nts
of core believed to be important for the IRES function
were included (Lemon and Honda, 1997). Top line: the
sequence of the infectious genotype 1a clone pCV-H77C
(Yanagi et al., 1997). Bottom line: the sequence of the
infectious genotype 2a clone pJ6CF. Dot: identity with
the sequence of H77C. Capital letter: different from the
sequence of H77C. Dash: deletion. Bold face: initiation
or stop codon of the ORF. Underlined: *AgeI* cleavage
site. Arrow: putative sites in the HCV polyprotein
cleaved by host signal peptidases. Numbering
corresponds to the sequence of pCV-H77C.

Figures 6A-6F show the nucleotide sequence of
the infectious hepatitis C virus clone of genotype 1a
strain H77C and Figures 6G-6H show the amino acid
sequence encoded by the clone.

Figures 7A-7F show the nucleotide sequence of
the infectious hepatitis C virus clone of genotype 1b
strain HC-J4 and Figures 7G-H show the amino acid
sequence encoded by the clone.

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DESCRIPTION OF THE INVENTION

The present invention relates to nucleic acid sequence which comprises the genome of an infectious hepatitis C virus. More specifically, the invention relates to nucleic acid sequence which encodes infectious hepatitis C virus of strain HC-J6_{CH}, genotype 2a. The infectious nucleic acid sequence of the invention is shown in SEQ ID NO:1 and is contained in a plasmid construct deposited with the American Type Culture Collection (ATCC) on May 28, 1999 and having ATCC accession number PTA-153.

The invention also relates to "chimeric nucleic acid sequences" where the chimeric nucleic acid sequences consist of open-reading frame sequences and/or 5' and/or 3' untranslated sequences taken from nucleic acid sequences of hepatitis C viruses of different genotypes or subtypes.

In one embodiment, the chimeric nucleic acid sequence consists of sequence from the genome of infectious HCV of genotype 2a which encodes structural polypeptides and sequence from the genome of a HCV of a different genotype or subtype which encodes nonstructural polypeptides.

Alternatively, the nonstructural region of infectious HCV of genotype 2a and structural region of a HCV of a different genotype or subtype may be combined. This will result in a chimeric nucleic acid sequence consisting of sequence from the genome of infectious HCV of genotype 2a which encodes nonstructural polypeptides and sequence from the genome of a HCV of a another genotype or subtype which encodes structural polypeptides.

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Preferably, the nucleic acid sequence from the genome of the infectious HCV clone of genotype 1a (deposited with the ATCC on June 2, 1999 ; Figures 6A-6F), or the nucleic acid sequence from the genome of the infectious HCV clone of genotype 1b (ATCC accession
5 number 209596; Figures 7A-7F) is used to construct the chimeric nucleic acid sequence with the HCV of genotype 2a of the invention.

10 It is believed that the construction of such chimeric nucleic acid sequences will be of importance in studying the growth and virulence properties of hepatitis C virus and in the production of candidate hepatitis C virus vaccines suitable to confer protection
15 against multiple genotypes of HCV. For example, one might produce a "multivalent" vaccine by putting epitopes from several genotypes or subtypes into one clone. Alternatively one might replace just a single
20 gene from an infectious sequence with the corresponding gene from the genomic sequence of a strain from another genotype or subtype or create a chimeric gene which contains portions of a gene from two genotypes or
25 subtypes. Examples of genes which could be replaced or which could be made chimeric, include, but are not limited to, the E1, E2 and NS4 genes.

The invention further relates to mutations of the infectious nucleic acid sequences where "mutations"
30 include, but are not limited to, point mutations, deletions and insertions. Of course, one of ordinary skill in the art would recognize that the size of the insertions would be limited by the ability of the resultant nucleic acid sequence to be properly packaged
35 within the virion. Such mutations could be produced by

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techniques known to those of skill in the art such as site-directed mutagenesis, fusion PCR, and restriction digestion followed by religation.

In one embodiment, mutagenesis might be undertaken to determine sequences that are important for viral properties such as replication or virulence. For example, one may introduce a mutation into the infectious nucleic acid sequence which eliminates the cleavage site between the NS4A and NS4B polypeptides to examine the effects on viral replication and processing of the polypeptide.

Alternatively, one may delete all or part of a gene or of the 5' or 3' nontranslated region contained in an infectious nucleic acid sequence and then transfect a host cell (animal or cell culture) with the mutated sequence and measure viral replication in the host by methods known in the art such as RT-PCR. Preferred genes include, but are not limited to, the P7, NS4B and NS5A genes. Of course, those of ordinary skill in the art will understand that deletion of part of a gene, preferably the central portion of the gene, may be preferable to deletion of the entire gene in order to conserve the cleavage site boundaries which exist between proteins in the HCV polyprotein and which are necessary for proper processing of the polyprotein.

In the alternative, if the transfection is into a host animal such as a chimpanzee, one can monitor the virulence phenotype of the virus produced by transfection of the mutated infectious nucleic acid sequence by methods known in the art such as measurement of liver enzyme levels (alanine aminotransferase (ALT) or isocitrate dehydrogenase (ICD)) or by histopathology

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° of liver biopsies. Thus, mutations of the infectious nucleic acid sequences may be useful in the production of attenuated HCV strains suitable for vaccine use.

5 The invention also relates to the use of the infectious nucleic acid sequence of the present invention to produce attenuated viral strains via passage in vitro or in vivo of the virus produced by transfection with the infectious nucleic acid sequence.

10 The present invention therefore relates to the use of the nucleic acid sequence of the invention to identify cell lines capable of supporting the replication of HCV.

15 In particular, it is contemplated that the mutations of the infectious nucleic acid sequence of the invention and the production of chimeric sequences as discussed above may be useful in identifying sequences critical for cell culture adaptation of HCV and hence, may be useful in identifying cell lines capable of
20 supporting HCV replication.

Transfection of tissue culture cells with the nucleic acid sequences of the invention may be done by methods of transfection known in the art such as
25 electroporation, precipitation with DEAE-Dextran or calcium phosphate or liposomes.

In one such embodiment, the method comprises the growing of animal cells, especially human cells, in vitro and transfecting the cells with the nucleic acid
30 of the invention, then determining if the cells show indicia of HCV infection. Such indicia include the detection of viral antigens in the cell, for example, by immunofluorescence procedures well known in the art; the
35 detection of viral polypeptides by Western blotting

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using antibodies specific therefor; and the detection of newly transcribed viral RNA within the cells via methods such as RT-PCR. The presence of live, infectious virus particles following such tests may also be shown by injection of cell culture medium or cell lysates into healthy, susceptible animals, with subsequent exhibition of the signs and symptoms of HCV infection.

Suitable cells or cell lines for culturing HCV include, but are not limited to, lymphocyte and hepatocyte cell lines known in the art.

Alternatively, primary hepatocytes can be cultured, and then infected with HCV; or, the hepatocyte cultures could be derived from the livers of infected chimpanzees. In addition, various immortalization methods known to those of ordinary skill in the art can be used to obtain cell lines derived from hepatocyte cultures. For example, primary hepatocyte cultures may be fused to a variety of cells to maintain stability.

The present invention further relates to the in vitro and in vivo production of hepatitis C viruses from the nucleic acid sequences of the invention.

In one embodiment, the sequences of the invention can be inserted into an expression vector that functions in eukaryotic cells. Eukaryotic expression vectors suitable for producing high efficiency gene transfer in vivo are well known to those of ordinary skill in the art and include, but are not limited to, plasmids, vaccinia viruses, retroviruses, adenoviruses and adeno-associated viruses.

In another embodiment, the sequences contained in the recombinant expression vector can be transcribed in vitro by methods known to those of ordinary skill in

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° the art in order to produce RNA transcripts which encode the hepatitis C viruses of the invention. The hepatitis C viruses of the invention may then be produced by transfecting cells by methods known to those of ordinary skill in the art with either the in vitro transcription mixture containing the RNA transcripts or with the recombinant expression vectors containing the nucleic acid sequences described herein.

10 The hepatitis C viruses produced from the sequences of the invention may be purified or partially purified from the transfected cells by methods known to those of ordinary skill in the art. In a preferred embodiment, the viruses are partially purified prior to their use as immunogens in the pharmaceutical compositions and vaccines of the present invention.

20 The present invention therefore relates to the use of the hepatitis C viruses produced from the nucleic acid sequences of the invention as immunogens in live or killed (e.g., formalin inactivated) vaccines to prevent hepatitis C in a mammal.

25 In an alternative embodiment, the immunogen of the present invention may be an infectious nucleic acid sequence, a chimeric nucleic acid sequence, or a mutated infectious nucleic acid sequence which encodes a hepatitis C virus. Where the sequence is a cDNA sequence, the cDNAs and their RNA transcripts may be used to transfect a mammal by direct injection into the liver tissue of the mammal as described in the Examples.

30 Alternatively, direct gene transfer may be accomplished via administration of a eukaryotic expression vector containing a nucleic acid sequence of the invention.

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In yet another embodiment, the immunogen may be a polypeptide encoded by the nucleic acid sequences of the invention. The present invention therefore also relates to polypeptides produced from the nucleic acid sequences of the invention or fragments thereof. In one embodiment, polypeptides of the present invention can be recombinantly produced by synthesis from the nucleic acid sequences of the invention or isolated fragments thereof, and purified, or partially purified, from transfected cells using methods already known in the art. In an alternative embodiment, the polypeptides may be purified or partially purified from viral particles produced via transfection of a host cell with the nucleic acid sequences of the invention. Such polypeptides might, for example, include either capsid or envelope polypeptides prepared from the sequences of the present invention.

When used as immunogens, the nucleic acid sequences of the invention, or the polypeptides or viruses produced therefrom, are preferably partially purified prior to use as immunogens in pharmaceutical compositions and vaccines of the present invention.

When used as a vaccine, the sequences and the polypeptide and virus products thereof, can be administered alone or in a suitable diluent, including, but not limited to, water, saline, or some type of buffered medium. The vaccine according to the present invention may be administered to an animal, especially a mammal, and most especially a human, by a variety of routes, including, but not limited to, intradermally, intramuscularly, subcutaneously, or in any combination thereof.

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Suitable amounts of material to administer for prophylactic and therapeutic purposes will vary depending on the route selected and the immunogen (nucleic acid, virus, polypeptide) administered. One skilled in the art will appreciate that the amounts to be administered for any particular treatment protocol can be readily determined without undue experimentation. The vaccines of the present invention may be administered once or periodically until a suitable titer of anti-HCV antibodies appear in the blood. For an immunogen consisting of a nucleic acid sequence, a suitable amount of nucleic acid sequence to be used for prophylactic purposes might be expected to fall in the range of from about 100 µg to about 5 mg and most preferably in the range of from about 500 µg to about 2mg. For a polypeptide, a suitable amount to use for prophylactic purposes is preferably 100 ng to 100 µg and for a virus 10^2 to 10^6 infectious doses. Such administration will, of course, occur prior to any sign of HCV infection.

A vaccine of the present invention may be employed in such forms as capsules, liquid solutions, suspensions or elixirs for oral administration, or sterile liquid forms such as solutions or suspensions. An inert carrier is preferably used, such as saline or phosphate-buffered saline, or any such carrier in which the HCV of the present invention can be suitably suspended. The vaccines may be in the form of single dose preparations or in multi-dose flasks which can be utilized for mass-vaccination programs of both animals and humans. For purposes of using the vaccines of the present invention reference is made to Remington's

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5 Pharmaceutical Sciences, Mack Publishing Co., Easton, Pa., Osol (Ed.) (1980); and New Trends and Developments in Vaccines, Voller et al. (Eds.), University Park Press, Baltimore, Md. (1978), both of which provide much
10 useful information for preparing and using vaccines. Of course, the polypeptides of the present invention, when used as vaccines, can include, as part of the composition or emulsion, a suitable adjuvant, such as
15 alum (or aluminum hydroxide) when humans are to be vaccinated, to further stimulate production of antibodies by immune cells. When nucleic acids, viruses or polypeptides are used for vaccination purposes, other specific adjuvants such as CpG motifs (Krieg, A.K. et al. (1995) and (1996)), may prove useful.

 When the nucleic acids, viruses and polypeptides of the present invention are used as vaccines or inocula, they will normally exist as
20 physically discrete units suitable as a unitary dosage for animals, especially mammals, and most especially humans, wherein each unit will contain a predetermined quantity of active material calculated to produce the desired immunogenic effect in association with the
25 required diluent. The dose of said vaccine or inoculum according to the present invention is administered at least once. In order to increase the antibody level, a second or booster dose may be administered at some time after the initial dose. The need for, and timing of,
30 such booster dose will, of course, be determined within the sound judgment of the administrator of such vaccine or inoculum and according to sound principles well known in the art. For example, such booster dose could
35 reasonably be expected to be advantageous at some time

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° between about 2 weeks to about 6 months following the initial vaccination. Subsequent doses may be administered as indicated.

5 The nucleic acid sequences, viruses and polypeptides of the present invention can also be administered for purposes of therapy, where a mammal, especially a primate, and most especially a human, is already infected, as shown by well known diagnostic measures. When the nucleic acid sequences, viruses or
10 polypeptides of the present invention are used for such therapeutic purposes, much of the same criteria will apply as when it is used as a vaccine, except that inoculation will occur post-infection. Thus, when the
15 nucleic acid sequences, viruses or polypeptides of the present invention are used as therapeutic agents in the treatment of infection, the therapeutic agent comprises a pharmaceutical composition containing a sufficient
20 amount of said nucleic acid sequences, viruses or polypeptides so as to elicit a therapeutically effective response in the organism to be treated. Of course, the amount of pharmaceutical composition to be administered will, as for vaccines, vary depending on the immunogen
25 contained therein (nucleic acid, polypeptide, virus) and on the route of administration.

The therapeutic agent according to the present invention can thus be administered by subcutaneous, intramuscular or intradermal routes. One skilled in the
30 art will certainly appreciate that the amounts to be administered for any particular treatment protocol can be readily determined without undue experimentation. Of course, the actual amounts will vary depending on the
35 route of administration as well as the sex, age, and

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clinical status of the subject which, in the case of human patients, is to be determined with the sound judgment of the clinician.

The therapeutic agent of the present invention can be employed in such forms as capsules, liquid solutions, suspensions or elixirs, or sterile liquid forms such as solutions or suspensions. An inert carrier is preferably used, such as saline, phosphate-buffered saline, or any such carrier in which the HCV of the present invention can be suitably suspended. The therapeutic agents may be in the form of single dose preparations or in the multi-dose flasks which can be utilized for mass-treatment programs of both animals and humans. Of course, when the nucleic acid sequences, viruses or polypeptides of the present invention are used as therapeutic agents they may be administered as a single dose or as a series of doses, depending on the situation as determined by the person conducting the treatment.

The nucleic acids, polypeptides and viruses of the present invention can also be utilized in the production of antibodies against HCV. The term "antibody" is herein used to refer to immunoglobulin molecules and immunologically active portions of immunoglobulin molecules. Examples of antibody molecules are intact immunoglobulin molecules, substantially intact immunoglobulin molecules and portions of an immunoglobulin molecule, including those portions known in the art as Fab, F(ab')₂ and F(v) as well as chimeric antibody molecules.

Thus, the polypeptides, viruses and nucleic acid sequences of the present invention can be used in

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° the generation of antibodies that immunoreact (i.e., specific binding between an antigenic determinant-containing molecule and a molecule containing an antibody combining site such as a whole antibody molecule or an active portion thereof) with antigenic determinants on the surface of hepatitis C virus particles.

10 The present invention therefore also relates to antibodies produced following immunization with the nucleic acid sequences, viruses or polypeptides of the present invention. These antibodies are typically produced by immunizing a mammal with an immunogen or vaccine to induce antibody molecules having

15 immunospecificity for polypeptides or viruses produced in response to infection with the nucleic acid sequences of the present invention. When used in generating such antibodies, the nucleic acid sequences, viruses, or polypeptides of the present invention may be linked to

20 some type of carrier molecule. The resulting antibody molecules are then collected from said mammal. Antibodies produced according to the present invention have the unique advantage of being generated in response

25 to authentic, functional polypeptides produced according to the actual cloned HCV genome.

The antibody molecules of the present invention may be polyclonal or monoclonal. Monoclonal antibodies are readily produced by methods well known in

30 the art. Portions of immunoglobulin molecules, such as Fabs, as well as chimeric antibodies, may also be produced by methods well known to those of ordinary skill in the art of generating such antibodies.

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The antibodies according to the present invention may also be contained in blood, plasma, serum, hybridoma supernatants, and the like. Alternatively, the antibody of the present invention is isolated to the extent desired by well known techniques such as, for example, using DEAE Sephadex. The antibodies produced according to the present invention may be further purified so as to obtain specific classes or subclasses of antibody such as IgM, IgG, IgA, and the like. Antibodies of the IgG class are preferred for purposes of passive protection.

The antibodies of the present invention are useful in the prevention and treatment of diseases caused by hepatitis C virus in animals, especially mammals, and most especially humans.

In providing the antibodies of the present invention to a recipient mammal, preferably a human, the dosage of administered antibodies will vary depending on such factors as the mammal's age, weight, height, sex, general medical condition, previous medical history, and the like.

In general, it will be advantageous to provide the recipient mammal with a dosage of antibodies in the range of from about 1 mg/kg body weight to about 10 mg/kg body weight of the mammal, although a lower or higher dose may be administered if found desirable. Such antibodies will normally be administered by intravenous or intramuscular route as an inoculum. The antibodies of the present invention are intended to be provided to the recipient subject in an amount sufficient to prevent, lessen or attenuate the severity, extent or duration of any existing infection.

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° The antibodies prepared by use of the nucleic acid sequences, viruses or polypeptides of the present invention are also highly useful for diagnostic purposes. For example, the antibodies can be used as in
5 vitro diagnostic agents to test for the presence of HCV in biological samples taken from animals, especially humans. Such assays include, but are not limited to, radioimmunoassays, EIA, fluorescence, Western blot analysis and ELISAs. In one such embodiment, the
10 biological sample is contacted with antibodies of the present invention and a labeled second antibody is used to detect the presence of HCV to which the antibodies are bound.

15 Such assays may be, for example, direct where the labeled first antibody is immunoreactive with the antigen, such as, for example, a polypeptide on the surface of the virus; indirect where a labeled second
20 antibody is reactive with the first antibody; a competitive protocol such as would involve the addition of a labeled antigen; or sandwich where both labeled and unlabeled antibody are used, as well as other protocols well known and described in the art.

25 In one embodiment, an immunoassay method would utilize an antibody specific for HCV envelope determinants and would further comprise the steps of contacting a biological sample with the HCV-specific
30 antibody and then detecting the presence of HCV material in the test sample using one of the types of assay protocols as described above. Polypeptides and antibodies produced according to the present invention may also be supplied in the form of a kit, either
35 present in vials as purified material, or present in

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compositions and suspended in suitable diluents as previously described.

In a preferred embodiment, such a diagnostic test kit for detection of HCV antigens in a test sample comprises in combination a series of containers, each container a reagent needed for such assay. Thus, one such container would contain a specific amount of HCV-specific antibody as already described, a second container would contain a diluent for suspension of the sample to be tested, a third container would contain a positive control and an additional container would contain a negative control. An additional container could contain a blank.

For all prophylactic, therapeutic and diagnostic uses, the antibodies of the invention and other reagents, plus appropriate devices and accessories, may be provided in the form of a kit so as to facilitate ready availability and ease of use.

The present invention also relates to the use of nucleic acid sequences and polypeptides of the present invention to screen potential antiviral agents for antiviral activity against HCV. Such screening methods are known by those of skill in the art.

Generally, the antiviral agents are tested at a variety of concentrations, for their effect on preventing viral replication in cell culture systems which support viral replication, and then for an inhibition of infectivity or of viral pathogenicity (and a low level of toxicity) in an animal model system.

In one embodiment, animal cells (especially human cells) transfected with the nucleic acid sequences of the invention are cultured in vitro and the cells are

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° treated with a candidate antiviral agent (a chemical, peptide etc.) by adding the candidate agent to the medium. The treated cells are then exposed, possibly under transfecting or fusing conditions known in the art, to the nucleic acid sequences of the present invention. A sufficient period of time would then be allowed to pass for infection to occur, following which the presence or absence of viral replication would be determined versus untreated control cells by methods known to those of ordinary skill in the art. Such methods include, but are not limited to, the detection of viral antigens in the cell, for example, by immunofluorescence procedures well known in the art; the detection of viral polypeptides by Western blotting using antibodies specific therefor; the detection of newly transcribed viral RNA within the cells by RT-PCR; and the detection of the presence of live, infectious virus particles by injection of cell culture medium or cell lysates into healthy, susceptible animals, with subsequent exhibition of the signs and symptoms of HCV infection. A comparison of results obtained for control cells (treated only with nucleic acid sequence) with those obtained for treated cells (nucleic acid sequence and antiviral agent) would indicate, the degree, if any, of antiviral activity of the candidate antiviral agent. Of course, one of ordinary skill in the art would readily understand that such cells can be treated with the candidate antiviral agent either before or after exposure to the nucleic acid sequence of the present invention so as to determine what stage, or stages, of viral infection and replication said agent is effective against.

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° In an alternative embodiment, viral enzyme such as NS3 protease, NS2-NS3 protease, NS3 helicase or NS5B RNA polymerase may be produced from a nucleic acid sequence of the invention and used to screen for inhibitors which may act as antiviral agents. The structural and nonstructural regions of the HCV genome, including nucleotide and amino acid locations, have been determined, for example, as depicted in Houghton, M. (1996), Fig. 1; and Major, M.E. et al. (1997), Table 2.

5 Such above-mentioned protease inhibitors may take the form of chemical compounds or peptides which mimic the known cleavage sites of the protease and may be screened using methods known to those of skill in the art (Houghton, M. (1996) and Major, M.E. et al. (1997)). For example, a substrate may be employed which mimics the protease's natural substrate, but which provides a detectable signal (e.g. by fluorimetric or colorimetric methods) when cleaved. This substrate is then incubated with the protease and the candidate protease inhibitor under conditions of suitable pH, temperature etc. to detect protease activity. The proteolytic activities of the protease in the presence or absence of the candidate inhibitor are then determined.

10 In yet another embodiment, a candidate antiviral agent (such as a protease inhibitor) may be directly assayed in vivo for antiviral activity by administering the candidate antiviral agent to a chimpanzee transfected with a nucleic acid sequence of the invention or infected with a virus of the invention and then measuring viral replication in vivo via methods such as RT-PCR. Of course, the chimpanzee may be treated with the candidate agent either before or after

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transfection with the infectious nucleic acid sequence or infected with a virus of the invention so as to determine what stage, or stages, of viral infection and replication the agent is effective against.

The invention also provides that the nucleic acid sequences, viruses and polypeptides of the invention may be supplied in the form of a kit, alone or in the form of a pharmaceutical composition.

All scientific publication and/or patents cited herein are specifically incorporated by reference. The following examples illustrate various aspects of the invention but are in no way intended to limit the scope thereof.

EXAMPLES

Materials and Methods

Source of HCV

An infectious plasma pool of HCV genotype 2a (HC-J6_{CH}) prepared from acute phase plasma of a chimpanzee experimentally inoculated with plasma from a Japanese patient infected with strain HC-J6 (Okamoto et al., 1991) was used for cloning. An infectious cDNA clone of HCV strain H77, genotype 1a was also used (pCV-H77C; Yanagi et al., 1997).

Amplification, cloning and sequence analysis

Viral RNA was extracted from 100 µl aliquots of the HC-J6_{CH} plasma pool with the TRIzol system (GIBCO/BRL) (Yanagi et al., 1997). Primers used in cDNA synthesis and PCR amplification were based on the genomic sequence of strain HC-J6 (Okamoto et al., 1991) and from the conserved region (3'X) of the 3' UTR of HCV genotype 2a (Tanaka et al., 1996) (Table 1). The RNA

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was denatured at 65°C for 2 min, and cDNA was synthesized at 42°C for 1 hour with Superscript II reverse transcriptase (GIBCO/BRL) and specific reverse primers in 20 µl reaction volumes. The cDNA mixtures were treated with RNase H and RNase T1 (GIBCO/BRL) at 37°C for 20 min.

TABLE 1

Oligonucleotides used for amplification and cloning of strain HC-J6_{CH}, genotype 2a

Designation	Sequence (5' → 3') ^a
2427S-H77	ACTGGACACGAGGTGGCCGCGTC
2426S-H77	TTGTTCTTGTCGGGTTAATGGCGC
2645R-H77	GGGTGTACTACACACATGAGTAAG
2832R-H77	AAGCGCCCCCTAACTGATGATG
H2751SII	CGTCATCGATACCTCAGCGGGCATATGCACTGGACACGGA
H2786R	GTCCAGTGCATATGCCCGCTGAGG
H2870R	CATGCACCAGCTGATATAGCGCTTGTAATATG
H7851S	TCCGTAGAGGAAGCTTGACGCTGACGCC
H9140S (M)	CAGAGGAGGCAGGGTGCTATATGTGGCAAGTAC
H9173R (M)	GTA CTTGCCACATATAGCAGCCCTGCCTCCTCTG
H9471R	CGTCTCTAGACAGGAAATGGCTTAAGAGGCCGAGTGTTTACC
J6-H2556S	TTATGGATGCTCATCTTGTTGGGCCAGGCCGAAGCAGCTTTGGAGAACCTCGTAATACTCAATGC
356RF-J6H	AGGATTTGTGCTCATGGTGACGGTCTACGAG
1S-J6 ^b	<i>TTTTTTTGGCGCGCTAAATACGACTCACTATAGACCCGCCCCCTAATAGG</i>
333S-J6	CCGTGCACCATGAGCACAAATCCTAAACCTC
753R-J6	GGATGTACCCCATGAGGTGCGCAAAG
2543S-J6F	GTTTGCGCCTGCTTATGGATGCTCATCTTG
2787R-J6(26)	GCGTCATAAGCATATGCCTGTTGGGG
3329R-J6	CCCTCAGCACTGGAGTACATCTG
5487-J6F	CGTCATGCATACCCCTAGGCGGCTCTCATTGAAGAGGG
5518R-J6F	CGTCCCCTCTTCAATGAGAGCGCTCTAGA
9251S-J6F	GCGGTGAAGACCAAGCTCAAACCTCACTC
9305R-J6F	AATCTAGAAGGCGGCTTCCGGCAATGGAGTGAGTTGAGC
9310R-J6F	CGTCTCTAGAGGATAAATCCAGGAGGCGGCTTCCGGC
9399S-J6F	TACTTTTGTAGGGGTAGGCCTTTTCC
9464-J6F	CGTCTCTAGAGTGTAGCTAATGTGTGCCGCTCTA
9470(24)-J6	CTATGGAGTGTAGCTAATGTGTGC
J6-3' XR	CGTCTCTAGACATGATCTGCAGAGAGACAGTTACGGCACTCTCTGFCAGTCATGCGGC TCACGGACCTTTCACAGCTAGCCGTGACTAGGGCTAAGATGGAGCCACC

^a HCV-specific sequences are shown in plain text, non HCV-specific sequences are shown in bold face, and cleavage sites used for cDNA cloning are underlined.

^b The core sequence of the T7 promotor is shown in italics.

The strategy used to amplify and clone the full-length HC-J6_{CH} sequence is shown in Fig. 1.

Nucleotide positions correspond to those of the 2a

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infectious clone (pJ6CF) that is described herein. The 5' end of HC-J6_{CH} (nts. 17-297, excluding primer sequences) was amplified from 2 µl of cDNA synthesized with primer a-2 (Yanagi et al., 1996). PCR was performed with *AmpliTag Gold* DNA polymerase (Perkin-Elmer) as described previously (Yanagi et al., 1996) using primers 1S-J6F and a-2. After purification, the amplified products were cloned into pGEM-T Easy vector (Promega) using standard procedures and 5 clones (pJ6-5'UTR) were sequenced.

The 3' end of HC-J6_{CH} was amplified in 3 overlapping pieces. RT-PCR of a short fragment of NS5B (nts. 9279-9439) was performed with primers 9251S-J6F and 9464R-J6F as described above. The PCR products were cloned into pGEM-T Easy vector and sequence analysis was performed from 5 pJ6-3'F clones. A second region spanning from NS5B to the conserved region of the 3' UTR (nts. 9376-9629) was amplified in RT-nested PCR (external primers H9261F and H3'X58R, internal primers H9282F and H3'X45R) (Yanagi et al., 1997). The amplified products were cloned into pGEM-9zf(-) by using *HindIII* and *XbaI* sites and 14 pJ6-3'VR clones were sequenced. The third fragment, which included the 3' terminal sequence was amplified with primers 9399S-J6F and J6-3'XR from one of the pJ6-3'VR clones, and cloned into one of the pJ6-3'F clones by using *StuI* and *XbaI* sites (pJ6-3'X).

The ORF of HCV HC-J6_{CH} was amplified by long RT-PCR in 3 overlapping pieces. The amplification was performed on 2 µl of the cDNA mixtures with the Advantage cDNA polymerase mix (Clontech) (Yanagi et al., 1997). The J6S fragment (nts. 86-2761) was amplified

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with primers a-1 (Yanagi et al., 1996) and J6-2787R from cDNA synthesized with primer J6-3329R. A single PCR round was performed in a Robocycler thermal cycler (Stratagene), and consisted of denaturation at 99°C for 35 sec, annealing at 67°C for 30 sec and elongation at 68°C for 4 min 30 sec during the first 5 cycles, 5 min during the next 10 cycles, 5 min 30 sec during the following 10 cycles and 6 min during the last 10 cycles. The J6B fragment (nts. 2573-5488) was amplified with primers 2543S-J6F and 5518R-J6F from cDNA synthesized with primer 5518R-J6F. Finally, the J6A fragment (nts. 5515-9282) was amplified with primers 5487S-J6F and 9310R-J6F from cDNA synthesized with primer 9470R(24)-J6F. PCR amplifications of fragments J6B and J6A consisted of denaturation at 99°C for 35 sec, annealing at 67°C for 30 sec and elongation at 68°C for 6 min during the first 5 cycles, 7 min during the next 10 cycles, 8 min during the following 10 cycles and 9 min during the last 10 cycles.

After purification of the long PCR products with QIAquick PCR purification kit (QIAGEN), A-tailing reactions were performed with *AmpliTag* DNA polymerase (Perkin Elmer) at 72 °C for 1 hour. The gel-purified A-tailed PCR products were cloned into pCR2.1 vector (Invitrogen) or pGEM-T Easy vector (Promega). DH5-alpha competent cells (GIBCO BRL) were transformed and selected on LB agar plates containing 100 µg/ml ampicillin (SIGMA) and amplified in LB liquid cultures at 30°C for 18 - 20 hrs (Yanagi et al., 1997). Midiprep was performed using Wizard *Plus* Midipreps DNA

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Purification System (Promega). Multiple clones of the J6S, J6A and the J6B fragments were sequenced.

The consensus sequence of strain HC-J6_{CH} (nts. 17-9629) was determined by direct sequencing of PCR products (nts. 297-3004 and nts. 4893-5762) and by sequence analysis of the TA clones (nts. 17-5488 and nts. 5515-9629) (Fig. 1). Both strands of DNA were sequenced in all cases. Analyses of genomic sequences, including multiple sequence alignments and tree analyses, were performed with GeneWorks (Oxford Molecular Group) (Bukh et al., 1995).

Construction of chimeric cDNA clones of genotypes 1a & 2a

Four full-length intertypic chimeric cDNA clones were constructed (Figs. 4, 5A, 5B). In each clone the C, E1 and E2 genes encoded the consensus amino acid sequence of HC-J6_{CH}. The p7 protein was encoded either by the HC-J6_{CH} or pCV-H77C consensus sequence, and the NS proteins were all encoded by pCV-H77C genes. To engineer these cDNA clones, an *Nde*I site from pCV-H77C was first eliminated by a silent substitution (C to T) at position 9158. In brief, two fragments were amplified from pCV-H77C with primers H7851S and H9173R(M) and with primers H9140S(M) and H9417R (Table 3), gel-purified and used for fusion PCR with primers H7851S and H9417R. The fusion PCR products were cloned into pCV-H77C by using *Hind*III and *Afl*III sites. A new artificial *Nde*I site was introduced by a silent substitution (C to T) at position 2765. PCR products, which were amplified from pCV-H77C with primer H2751SII containing artificial *Cla*I and *Nde*I sites and primer H2870R, were cloned into the modified pCV-H77C by using

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ClaI and Eco47III sites. The final construct (pH77CV) was used as a cassette vector to construct the intertypic chimeric HCV cDNA clones.

The four chimeric cDNA clones were constructed as follows. pH77CV-J6S (nucleotide sequence shown in SEQ ID No:3 and amino acid sequence shown in SEQ ID No:4): The AgeI/BsmI fragment of clone J6S2 and the BsmI/NdeI fragment of clone J6S1, were cloned into pH77CV by using AgeI and NdeI sites; pH77 (p7)CV-J6S (nucleotide sequence shown in SEQ ID No:5 and amino acid sequence shown in SEQ ID No:6): A fragment of pH77CV-J6S was replaced with a fragment amplified from pCV-H77C with primers J6-H2556S and H2786R by using BsaBI and NdeI sites; J6S (nucleotide sequence shown in SEQ ID No:7 and amino acid sequence shown in SEQ ID No:8): A fragment amplified from pH77pCV-H77C with primers a-1 and 356RF-J6H77 and another fragment amplified from pH77CV-J6S with primers 333S-J6 and 753R-J6 were gel-purified and a fusion-PCR was performed with primers a-1 and 753R-J6. The AgeI/ClaI fragment of the subcloned fusion PCR products and the ClaI/NdeI fragment of pH77CV-J6S were cloned into pH77CV-J6S by using AgeI and NdeI sites; pH77(p7)-J6S (nucleotide sequence shown in SEQ ID No:9 and amino acid sequence shown in SEQ ID No:10): The AgeI/ClaI fragment of J6S and the ClaI/NdeI fragment of (p7)CV-J6S were cloned into pH77(p7)CV-J6S by using AgeI and NdeI sites.

Each intertypic chimeric cDNA clone was retransformed to select a single clone, and large-scale preparation of plasmid DNA was performed with a QIAGEN plasmid Maxi kit as described previously (Yanagi et al., 1997). Each of the four cDNA clones was completely

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- ° sequenced before inoculation. Each clone was genetically stable since the digestion pattern was as expected following retransformation and the complete sequence was the expected one.

5 Construction of full-length cDNA clone HC-J6_{CH}

An overview of the full-length HC-J6_{CH} clone is presented in Fig. 1. In the final construct pJ6CF, which encodes the consensus polyprotein of HC-J6_{CH}, an XbaI site was eliminated by a silent substitution (A to G) at position 5494. Digested fragments containing the consensus sequence were purified from the appropriate subclones and ligated using the sites indicated. The full-length cDNA clone (pJ6CF) was retransformed to select a single clone, and large-scale preparation of plasmid DNA followed by the complete sequence analysis was performed. Clone pJ6CF was genetically stable.

20 Intrahepatic transfection of chimpanzee with transcribed RNA

In duplicate 100 µl reactions, RNA was transcribed *in vitro* with T7 RNA polymerase (Promega) from 10 µg of template plasmid linearized with XbaI (Promega) as described previously (Yanagi et al., 1997). The integrity of the RNA was checked by electrophoresis through agarose gel stained with ethidium bromide (Yanagi et al., 1997). Each transcription mixture was diluted with 400 µl of ice-cold phosphate-buffered saline without calcium or magnesium and then immediately frozen on dry ice and stored at -80°C. Within 24 hours, both transcription mixtures were injected into the same chimpanzee by percutaneous intrahepatic injection guided by ultrasound (Yanagi et al., 1998, 1999). If the

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chimpanzee did not become infected, the same transfection was repeated once. After two negative results, the next clone was inoculated into the same chimpanzee following the same protocol. Injections were performed at weeks 0 and 2 with pH77CV-J6S, at weeks 5 and 8 with pH77(p7)CV-J6S, at weeks 14 and 16 with pH77-J6S, at weeks 19 and 23 with pH77(p7)-J6S, at week 28 with pJ6CF, and finally at week 34 with pCV-H77C. The chimpanzee was maintained under conditions that met or exceeded all requirements for its use in an approved facility.

Serum samples were collected weekly from the chimpanzee and monitored for liver enzyme levels by standard procedures, anti-HCV antibodies by the second-generation ELISA (Abbott) and HCV RNA by a sensitive RT-nested PCR assay with *AmpliTaq Gold* DNA polymerase using primers from the 5' UTR (Yanagi et al., 1996). Samples were scored as negative for HCV RNA if two independent tests on 100 µl of serum were negative. The genome equivalent (GE) titer of HCV in positive samples was determined by RT-nested PCR on 10-fold serial dilutions of the extracted RNA (Bukh et al., 1998). The consensus sequence of the complete ORF from the chimpanzee infected with RNA transcripts of pJ6CF was determined by direct sequencing of overlapping PCR products obtained by long RT-nested PCR as previously described (Yanagi et al., 1997) with HC-J6 specific primers. After the intrahepatic transfection with RNA transcripts of pCV-H77C, we performed H77(genotype 1a)-specific RT-nested PCR with primers 2427S-H77 and 2832R-H77 for the 1st round and with primers 2462S-H77 and 2645R-H77 for the 2nd round (Table 3). The

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° sensitivity of this assay was equivalent to that of the assay using 5' UTR primers when testing serum containing only H77, genotype 1a. The genome titer of genotype 1a was determined by using this specific RT- nested PCR on
5 10-fold serial dilutions of the extracted RNA.

EXAMPLE 1

Sequence analysis of HCV strain HC-J6_{CH}

10 As minor deviations from the consensus amino acid sequence were found previously to render full-length HCV cDNA clones noninfectious (Yanagi et al., 1997, 1998), the consensus sequence of the cloning source of genotype 2a (strain HC-J6_{CH}) was determined
15 prior to constructing any full-length clones. In brief, a plasma pool containing strain HC-J6_{CH} was prepared from acute phase plasmapheresis units collected from a chimpanzee experimentally infected with HC-J6 (Okamoto et al., 1991). The HCV genome titer of this pool was
20 10^{5.4} genome equivalents (GE)/ml (Quantiplex HCV RNA bDNA 2.0, Chiron) and the infectivity titer was 10⁴ chimpanzee infectious doses/ml.

25 The consensus sequence of the 5' UTR of HC-J6_{CH} (nts. 17-340) was deduced from 5 clones containing nts. 17-297 and 8 clones containing nts. 86-340. The 5' UTR of the various clones was highly conserved, but the consensus sequence of HC-J6_{CH} differed by 2 nucleotides
30 from that published previously for HC-J6 (Okamoto et al., 1991: C to T at position 36 and T to C at position 222).

35 The consensus sequence of 14 clones of the 3' UTR of HC-J6_{CH} indicated that the 39 nucleotide long variable region was highly conserved in this strain and

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° was identical to that previously published for HC-J6 (Okamoto *et al.*, 1991). The polypyrimidine tract varied greatly in length (84-164 nucleotides), and contained some conserved A residues. In the conserved region, the proximal 16 nucleotides were identical to those previously published for isolates of different HCV genotypes (Kolykhalov *et al.*, 1996; Tanaka *et al.*, 1996; Yamada *et al.*, 1996). The remaining 82 nucleotides of the conserved region were determined for other genotype 2a strains (Tanaka *et al.*, 1996) but not for HC-J6 or HC-J6_{CH}.

The ORF of HC-J6_{CH} was amplified in 3 fragments by RT-PCR (Fig. 1). Eight clones of the J6S fragment (nts. 86-2761), 6 clones of the J6B fragment (nts. 2573-5488) and 6 clones of the J6A fragment (nts. 5515-9298) were sequenced. PCR fragments containing nts. 5489-5514 were sequenced directly. A quasispecies was found at 243 nucleotide (2.7%) and 69 amino acid (2.3%) positions, scattered throughout the 9099 nts (3033 aa) of the ORF. However, the majority, 231 nucleotide substitutions, were detected only once and 71.6 % of these represented silent mutations. The 12 remaining nucleotide substitutions were each restricted to 2 clones and only 4 of these resulted in amino acid changes. The nucleotide difference among the J6S clones ranged from 0.1 - 1.3%, among the J6B clones it ranged from 0.1 - 0.3%, and it ranged from 0.2 - 4.0% among the J6A clones (Fig. 2). Three of 8 J6S clones, 4 of 6 J6B clones, and all 6 J6A clones had defective polyproteins due to nucleotide deletions, insertions or substitutions.

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° The sequences of clones of strain HC-J6_{CH} were relatively homogeneous. This was highlighted by the high degree of conservation among clones of the HVR1 (Fig. 3), a region frequently used to study the quasispecies of HCV (Bukh et al., 1995). An exception was the sequence of clone J6A1, which differed by about 4% from the other clones of this region (Fig. 2). Importantly, the consensus sequence of strain HC-J6_{CH} (nts. 17-9629) could be determined with no ambiguity at the nucleotide or deduced amino acid level. The difference between the consensus ORF sequence of HC-J6_{CH} from the experimentally infected chimpanzee and that of HC-J6 of the inoculum (Okamoto et al., 1991) was 4.1 % and 2.2 % at the nucleotide and deduced amino acid levels, respectively (Fig. 2, Table 2). Moreover, we found that 12 (44.4%) of the 27 amino acids constituting HVR1 differed between HC-J6_{CH} and HC-J6 (Fig. 3). Such diversities are greater than the < 2 % generally considered to comprise a quasispecies. In fact, these differences are equivalent to those found between the two prototype strains of HCV genotype 1a [strains HCV-1 (Choo et al., 1991) and H77 (Yanagi et al., 1997)]. These results indicated that HC-J6_{CH}, which represented the major species in the experimentally infected chimpanzee, was a minor species in the original inoculum.

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TABLE 2

Percent difference of nucleotide and predicted amino acid sequences between strain HC-J6 (Okamoto et al., 1991) and strain HC-J6_{CH} from acute phase plasma pool of a chimpanzee inoculated with HC-J6

Genome Region	nt.position ^a	% nt. difference	% a.a. difference
ORF	341-9439	4.1 (373/9099) ^b	2.2 (66/3033) ^b
5' UTR	17-340	0.6 (2/324)	
Core	341-913	0.5 (3/573)	0 (0/191)
E1	914-1489	4.3 (25/576)	2.1 (4/192)
HVR1	1490-1570	24.7 (20/81)	44.4 (12/27)
E2-HVR1	1571-2590	3.9 (40/1020)	3.2 (11/340)
p7	2591-2779	3.7 (7/189)	3.2 (2/63)
NS2	2780-3430	4.0 (26/651)	2.8 (6/217)
NS3	3431-5323	4.0 (76/1893)	0.8 (5/631)
NS4A	5324-5485	4.3 (7/162)	1.9 (1/54)
NS4B	5486-6268	3.7 (29/783)	0.4 (1/261)
NS5A	6269-7666	5.4 (75/1398)	3.4 (16/466)
NS5B	7667-9439	3.7 (65/1773)	1.4 (8/591)
3' UTR	9440-9481	0 (0/42)	

a The nucleotide positions correspond to those of the infectious full-length genotype 2a clone (pJ6CF).

b The numbers in parenthesis indicate the nucleotide or amino acid differences for each region.

Example 2

Chimeric molecular clones

As chimeric flaviviruses with substituted structural genes have been useful in defining the biological function of viral sequences or proteins, in analyzing immune responses and in generating attenuated vaccine candidates (Bray and Lai, 1991; Chambers et al., 1999; Pletnev et al., 1992, 1993, 1998). The consensus sequence of the 2a structural genes and surrounding region was substituted for that of the infectious 1a cDNA clone. In the genotype 1a backbone, two silent mutations were introduced for cloning purposes [at positions 2765 (p7) and 9158 (NS5B) of pCV-H77C] (Fig. 4). The complete sequence of each chimera was verified. Infectivity of RNA transcripts from four different

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intertypic chimeric clones (Figs. 4, 5A, 5B) was evaluated by consecutive intrahepatic transfections of a chimpanzee. Clones were considered not to be viable if viral RNA was not detected in the serum within two weeks of the repeat transfection. All chimeric clones contained the C, E1 and E2 genes of genotype 2a. The two chimeric clones tested initially differed from each other in that one had the p7 gene of 2a (pH77CV-J6S) and the other [pH77(p7)CV-J6S] the p7 gene of 1a. They differed from the two other clones in that the 186 nucleotides of the 5' UTR just upstream of the initiation codon were from the 2a genotype. Since neither clone containing the chimeric 5' UTR was infectious, the chimeric 5' UTR was replaced with the consensus genotype 1a 5' UTR to generate the two p7 varieties [pH77-J6S and pH77(p7)-J6S]. After consecutive transfection of the four clones, no HCV RNA, anti-HCV or ALT elevation was detected in the chimpanzee during 28 weeks of follow-up, suggesting that RNA transcripts from these intertypic chimeric clones were not viable *in vivo*.

This finding that the intertypic clones between genotypes 1a and 2a were not viable was surprising since flavivirus chimeras containing the structural region of dengue virus type 1 or 2 or of tick-borne encephalitis virus and the nonstructural region of an infectious dengue type 4 virus were viable (Bray and Lai, 1991; Pletnev *et al.*, 1992, 1993). While considerable sequence variation exists between the infectious genotype 1a and 2a clones of HCV (Table 3), these viruses exhibit a higher degree of genetic heterogeneity than do the major genotypes of HCV. For other flaviviruses, however, it was possible to obtain

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infectious chimeric clones only if the capsid region was derived from the backbone cDNA clone (Chambers et al., 1999; Pletnev and Men, 1998).

TABLE 3

Percent difference of the amino acid sequences between the infectious clone of genotype 1a (pCV-H77C; Yanagi et al., 1997) and the infectious clone of genotype 2a (pJ6CF) of hepatitis C virus

Genome Region ^a	% difference
Polyprotein	27.9 (839/3007) ^b
Core	8.9 (17/191)
E1	37.0 (71/192)
HVR1	59.3 (16/27)
E2-HVR1	27.1 (91/336)
p7	38.1 (24/63)
NS2	41.9 (91/217)
NS3	19.2 (121/631)
NS4A	33.3 (18/54)
NS4B	26.8 (70/261)
NS5A	38.5 (171/444)
NS5B	25.2 (149/591)

^a Genome regions defined as in Table 1.

^b The numbers in parenthesis indicate the amino acid differences for each region. Positions with deletions or insertions in E2 (4 aa positions) and NS5A (26 aa positions) were not considered.

Trivial explanations may account for the lack of viability of these intertypic chimeras. First, the two silent mutations introduced in the genotype 1a backbone (one in p7 and one in NS5B) for cloning purposes could potentially eliminate infectivity. This is, however, very unlikely since mutations at these positions exist among field isolates of HCV including strain HC-J6_{CH} (Bukh et al., 1998). Also, it is noteworthy that the three previously published infectious clones of strain H77 had numerous silent nucleotide differences (Hong et al., 1999; Kolykhalov et al., 1997; Yanagi et al., 1997). Second, signal peptidases might not cleave the chimeric E2/p7 or p7/NS2

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junction. This seems unlikely, however, since
eukaryotic signal peptidases typically recognize the
amino acid sequences upstream of the cleavage site [the
(-3, -1) rule] (Nielsen et al., 1997) and the amino
acids at these two sites are conserved between genotypes
1a and 2a (Fig. 5B). Finally, the E2/p7 and/or p7/NS2
gene junctions could differ between genotypes 1a and 2a.
The junctions determined for genotypes 1a and 1b were
used (Lin et al., 1994; Mizushima et al., 1994; Selby et
al., 1994) because those for genotype 2a have not been
identified. In the latter two cases, further analyses
of genotype 2a should eventually provide sufficient data
to overcome such potential problems and it would most
likely be possible to construct a viable chimera.

More complicated explanations for the lack of
viability of the chimeras might be required if critical
genotype-specific interactions occur as regards the
structural proteins, the nonstructural proteins and the
genomic RNA. For instance, one cannot rule out that the
chimeras were not viable because the IRES function was
compromised. In *in vitro* studies the IRES activity
depended on RNA sequences not only in the 5' UTR but
also extending 3' of the translation initiation site
(Hahm et al., 1998; Lemon and Honda, 1997; Reynolds et
al., 1995). Although the 3' border of the HCV IRES is
still controversial it is believed to involve at most
the first 39 nts of the core gene (Lemon and Honda,
1997). The 5' UTR of the intertypic chimeras was either
a chimera of genotype 1a and 2a sequences or the entire
5' UTR was derived from the 1a clone (Figs. 4, 5A).
Importantly, the 5' end of core is conserved among
genotypes 1a and 2a (Fig. 5A). Thus, the predicted

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IRES-like secondary structure is maintained in these chimeras, suggesting that the IRES activity most likely was maintained.

Possible interactions between the structural proteins and the nonstructural proteins and/or the genomic RNA, which involve RNA packaging, replication or translation are conceivable. In poliovirus, which is another positive-sense RNA virus, functional coupling of RNA packaging to RNA replication and of RNA replication to translation have been suggested (Novak and Kirkegaard, 1994 ; Nugent et al., 1999). Similar to other viruses of the *Flaviviridae* family, a membrane-associated replicase complex is thought to initiate replication at the 3' end of HCV and to synthesize a complementary negative-strand RNA (Rice, 1996). The putative cis-acting elements at the 5' and 3' termini which are believed to be important for viral genome replication (Rice 1996; Frolov et al., 1998) should be maintained in the intertypic HCV chimeras at least in the two constructs with the authentic 1a 5'UTR. However, it is conceivable that the viral packaging system was interrupted (Frolov et al., 1998). Studies using a Kunjin flavivirus replicon system and providing the structural proteins *in trans* suggested that the essential encapsidation signals did not reside in the structural region of the genome (Khromykh et al., 1997, 1998). The location of the packaging signals of HCV is not known. However, if the structural proteins encapsidate viral RNA via genotype-specific sequences outside of the structural region, the chimeras would be unable to package the RNA and it might be extremely

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° difficult to construct viable chimeras between highly divergent strains.

Example 3

5 A consensus molecular clone of
 genotype 2a is infectious in vivo

 In order to prove that the genotype 2a portion
used in the 4 intertypic chimeric cDNA clones indeed
represented the infectious sequence, a consensus full-
10 length cDNA clone of HC-J6_{CH} (pJ6CF) was constructed.
The core sequence of the T7 promoter, a 5' guanosine
residue and the full-length sequence of HC-J6_{CH} (9711
nts) were cloned into pGEM-9Zf vector using NotI/XbaI
15 sites. Within the HCV sequence there were no deduced
amino acid differences and only 4 nucleotide differences
(at nucleotide positions 1822, 5494, 9247 and 9289) from
the consensus sequence of HC-J6_{CH} as determined in the
present study. The silent mutation at position 1822 was
20 within the structural region and so was also present in
the four intertypic chimeras. The 5' terminal 16 nts
and the 3' terminal 82 nts were deduced from previously
published HCV genotype 2a sequences (Okamoto et al.,
25 1991, Tanaka et al., 1996). The full-length cDNA clone
of genotype 2a contained a 5' UTR of 340 nts, an ORF of
9099 nts encoding 3033 amino acids and a 3' UTR
consisting of a variable region of 39 nts followed by a
132 nucleotide-long polypyrimidine tract interrupted
30 with 3 A residues and the 3' terminal conserved region
of 98 nts.

 RNA transcripts from pJ6CF were injected into
the same chimpanzee used for injection of the 4
35 intertypic chimeras. The chimpanzee became infected at

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the first attempt with an HCV titer of 10^2 GE/ml at week 1 post inoculation (p.i.), and 10^3 - 10^4 GE/ml during weeks 2 to 6 p.i. The consensus sequence of PCR products of the complete ORF, amplified from serum obtained during week 5 p.i., was identical to the sequence of pJ6CF and there was no evidence of a quasispecies. Since RNA transcripts of this infectious genotype 2a clone were infectious *in vivo*, and it shared an exact sequence with the non-infectious intertypic chimeric clones, their failure to replicate must have been the result of incompatibilities between the genotype 1a and 2a sequences.

To confirm that the chimpanzee used was susceptible also to infection by genotype 1a, which comprised most of the intertypic chimeras, the chimpanzee was subsequently inoculated with RNA transcripts from the infectious genotype 1a clone (pCV-H77C). Serum samples were tested in an H77-specific RT-PCR assay to identify super-infection with genotype 1a. At week 1 p.i. the total HCV genome titer was 10^4 GE/ml and the H77-specific (1a) genome titer was 10^2 GE/ml. The H77-specific genome titer increased to 10^3 GE/ml at week 2 p.i., and reached 10^4 GE/ml during weeks 3-6 p.i. The consensus sequence of PCR products amplified with H77-specific primers at weeks 1-6 p.i. were found to be identical to that of pCV-H77C. However, the direct sequences of PCR products amplified with the 5' UTR primers at weeks 1-2 after inoculation of pCV-H77C were identical to that of pJ6CF indicating that the 2a genotype was still present and represented the majority species. These experiments confirmed that the inability of the intertypic 1a, 2a

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° cDNA clones to infect the chimpanzee was not the result of protective immune responses in the chimpanzee but represented deficiencies intrinsic to the chimeras.

Discussion

5 The published infectious cDNA clones of HCV represent the two most important subtypes of genotype 1 (Hong et al., 1999; Kolykhalov et al., 1997; Yanagi et al., 1997, 1998). However, 5 more major genotypes of
10 HCV are recognized. In the above Examples, the infectivity of a cDNA clone of a second major HCV genotype was demonstrated. As in previous studies, the infectivity of RNA transcripts was demonstrated *in vivo*
15 by intrahepatic transfection of a chimpanzee. This new infectious clone (pJ6CF) encodes the consensus polyprotein of HCV strain HC-J6_{CH}, genotype 2a. Its encoded polyprotein differs from those of the infectious clones of genotypes 1a and 1b by approximately 30%
20 (Table 2). Genotype 2 strains, in particular subtypes 2a and 2b, have a worldwide distribution and important differences between genotypes 1 and 2 with respect to pathogenesis and treatment were indicated in previous
25 studies. The availability of an infectious clone representing a second major genotype of HCV should permit new ways of studying the molecular biology and immunopathology of this important and genetically quite different human pathogen.

30 The 5' and 3' UTRs of HCV are believed to be critical for viral replication, translation and viral packaging (Rice, 1996). The 5' 203 terminal nucleotides and the 3' 101 terminal nucleotides of the published
35 infectious clones of genotypes 1a and 1b were identical.

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However, the sequences of UTRs of the genotype 2a clone differ from those of the genotype 1 clones. Overall, the 5' UTR of the genotype 2a clone has 17 nt differences and a single nucleotide deletion compared with the infectious clones of genotype 1a (Fig. 5A). Five of these differences and the deletion are within the first 30 nucleotides, whereas the remainder are found within the predicted IRES structure. Differences also exist between the 3' UTR of the genotype 2a clone and the clones of genotype 1a (Fig. 5B). The sequences of the variable region are very different. Recent study has shown this region is not critical for infectivity *in vivo* (Yanagi *et al.*, 1999). Within the regions which are critical for infectivity *in vivo* (Yanagi *et al.*, 1999), the 132 nucleotide-long polypyrimidine tract of the genotype 2a clone has 3 unique A residues interspersed and the 3' terminal conserved region of 98 nts has 4 nt differences within the 3' terminal stable stem-loop structure (Fig. 5B) (Kolykhalov *et al.*, 1996; Tanaka *et al.*, 1996). Since the 2a clone was infectious these sequence differences are apparently real and are compatible with infectivity. Further studies are required to determine whether these represent critical genotype-specific sequences.

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WHAT IS CLAIMED IS:

1. A purified and isolated nucleic acid molecule which encodes human hepatitis C virus of genotype 2a, said molecule capable of expressing said virus when transfected into cells.
2. The nucleic acid molecule of claim 1, wherein said molecule encodes the amino acid sequence of SEQ ID NO:2.
3. The nucleic acid molecule of claim 2, wherein said molecule comprises the nucleic acid sequence of SEQ ID NO:1.
4. A DNA construct comprising a nucleic acid molecule according to claim 1.
5. A DNA construct comprising a nucleic acid molecule according to claim 3.
6. An RNA transcript of the DNA construct of claim 4.
7. An RNA transcript of the DNA construct of claim 5.
8. A cell transfected with the DNA construct of claim 4.
9. A cell transfected with the DNA construct of claim 5.
10. A cell transfected with RNA transcript of claim 6.

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11. A cell transfected with RNA transcript of claim 7.

12. A hepatitis C virus polypeptide produced by the cell of claims 8 or 9.

13. A hepatitis C virus polypeptide produced by the cell of claims 10 or 11.

14. A hepatitis C virus produced by the cell of claims 8 or 9.

15. A hepatitis C virus produced by the cell of claims 10 or 11.

16. A hepatitis C virus whose genome comprises a nucleic acid molecule according to claim 1.

17. A hepatitis C virus whose genome comprises a nucleic acid molecule according to claim 3.

18. A method for producing a hepatitis C virus comprising transfecting a host cell with the RNA transcript of claims 6 or 7.

19. A polypeptide encoded by a nucleic acid sequence according to claim 1.

20. A polypeptide encoded by a nucleic acid sequence according to claim 3.

21. The polypeptide of claim 19, wherein said polypeptide is selected from the group consisting of NS3 protease, E1 protein, E2 protein or NS4 protein.

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22. The polypeptide of claim 20, wherein said polypeptide is selected from the group consisting of NS3 protease, E1 protein, E2 protein or NS4 protein.

23. A method for assaying candidate antiviral agents for activity against HCV, comprising:

a) exposing a cell containing the hepatitis C virus of claims 16 or 17 to the candidate antiviral agent; and

b) measuring the presence or absence of hepatitis C virus replication in the cell of step (a).

24. The method of claim 23, wherein said replication in step (b) is measured by at least one of the following: negative strand RT-PCR, quantitative RT-PCR, Western blot, immunofluorescence, or infectivity in a susceptible animal.

25. A method for assaying candidate antiviral agents for activity against HCV, comprising:

a) exposing an HCV protease encoded by a nucleic acid sequence according to claims 1 or 3 or a fragment thereof to the candidate antiviral agent in the presence of a protease substrate; and

b) measuring the protease activity of said protease.

26. The method of claim 25, wherein said HCV protease is selected from the group consisting of an NS3 domain protease, an NS3-NS4A fusion polypeptide, or an NS2-NS3 protease.

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27. An antiviral agent identified as having antiviral activity for HCV by the method of claim 23.

28. An antiviral agent identified as having antiviral activity for HCV by the method of claim 25.

29. Antibody to the polypeptide of claim 19.

30. Antibody to the polypeptide of claim 20.

31. Antibody to the hepatitis C virus of claim 16.

32. Antibody to the hepatitis C virus of claim 17.

33. A method for determining the susceptibility of cells *in vitro* to support HCV infection, comprising the steps of:

- a) growing animal cells *in vitro*;
- b) transfecting into said cells the nucleic acid of claim 1; and
- c) determining if said cells show indicia of HCV replication.

34. The method according to claim 33, wherein said cells are human cells.

35. A composition comprising a polypeptide of claim 19 suspended in a suitable amount of a pharmaceutically acceptable diluent or excipient.

36. A composition comprising a polypeptide of claim 20 suspended in a suitable amount of a pharmaceutically acceptable diluent or excipient.

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37. A composition comprising a nucleic acid molecule of claim 1 suspended in a suitable amount of a pharmaceutically acceptable diluent or excipient.

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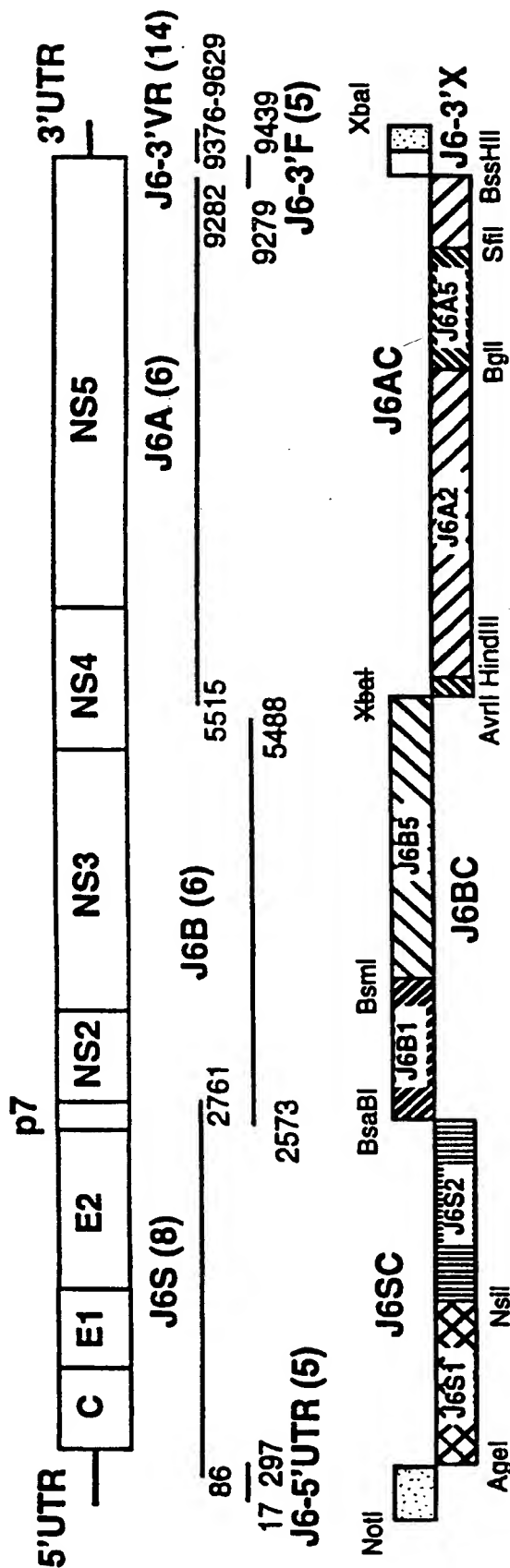
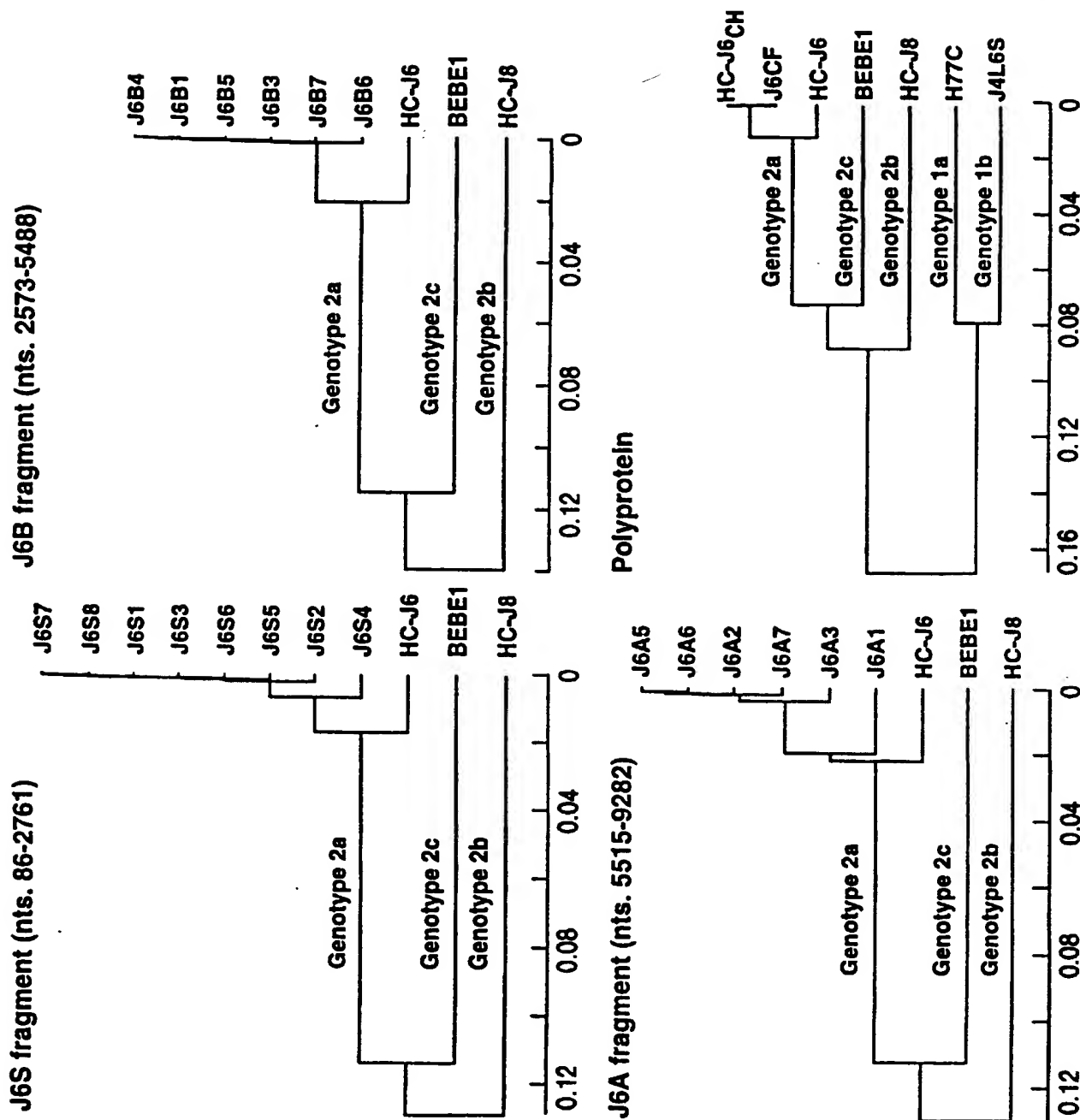


FIG. 1



FIG. 2





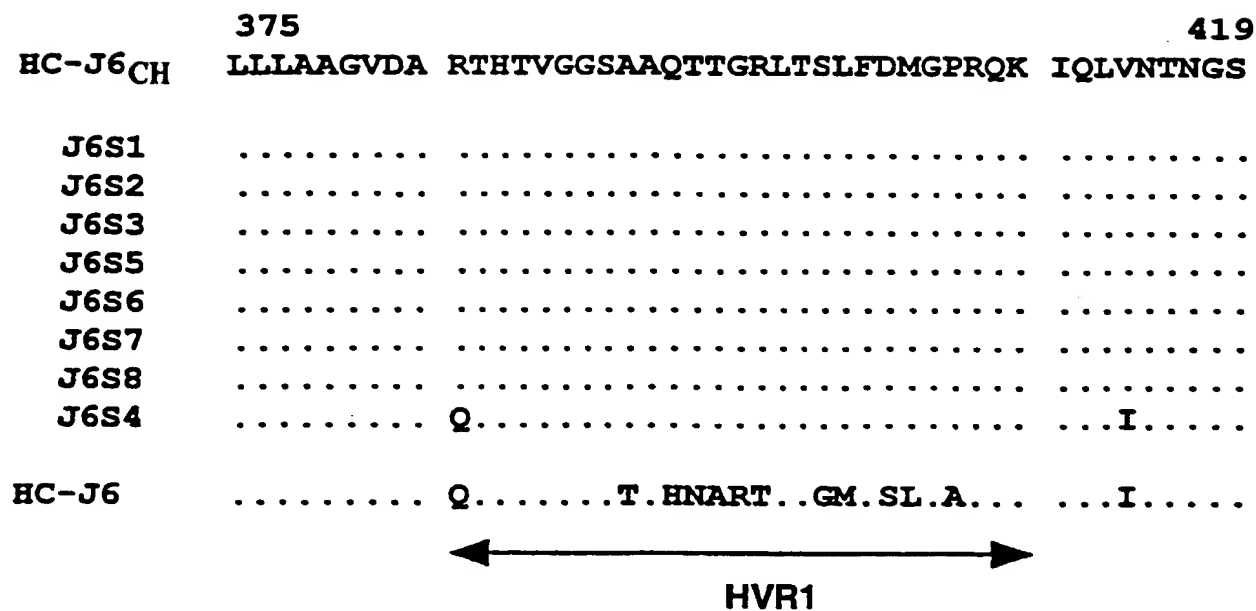


FIG. 3



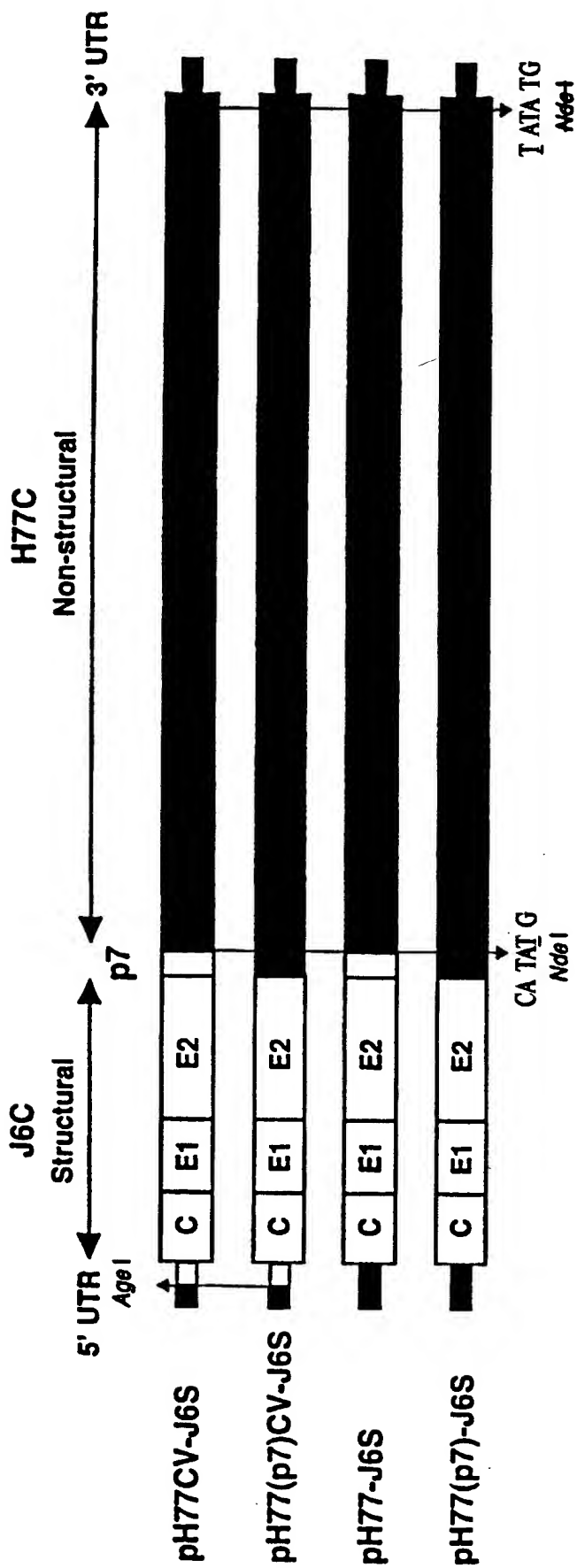


FIG. 4



5' Untranslated Region

FIG. 5A

	1	GCCAGCCCC	TGATGGGGC	GACACTCCAC	CATGAATCAC	TCCCCTGTGA	GGAAGTACTG	TCATCAGCGA	GAAAGCGTCT	AGCCATGGCG	90
H77C		
H77CV-J6S		
H77(p7)CV-J6S		
H77-J6S		
H77(p7)-J6S		
J6CF		A..C.....	..A..A.....G.	
	91	TTAGTATGAG	TGTGTCGAG	CCTCCAGGAC	CCCCCTCCC	GGGAGAGCCA	TAGTGTCTG	CGGAACCGGT	GAGTACACCG	GAATTGCCAG	180
H77C		
H77CV-J6S		
H77(p7)CV-J6S		
H77-J6S		
H77(p7)-J6S		
J6CF	A..C.	
	181	GACGACCGGG	TCCTTCTTG	GATAAACCG	CTCAATGCT	GGAGATTGG	GCGTGCCCC	GCAAGACTGC	TAGCCGAGTA	GTGTGGGTC	270
H77C		..A...T...G	...T...C	..CC.....	
H77CV-J6S		..A...T...G	...T...C	..CC.....	
H77(p7)CV-J6S		
H77-J6S		
H77(p7)-J6S		
J6CF		..A...T...G	...T...C	..CC.....	
	271	GCGAAGGCC	TTGTGGTACT	GCCTGATAGG	GTGCTTGCGA	GTGCCCCGG	AGGTCTCGTA	GACCGTGCAC	CATGAGCAGC	AATCCTAAAC	360
H77C		
H77CV-J6S		
H77(p7)CV-J6S		
H77-J6S		
H77(p7)-J6S		
J6CF		



FIG. 5B

3' Untranslated Region

9375
 H77C TGAAGGTTGG GGTAAACACT CCGGCCTCTT AAGCCATTTC CTG (Polypyrimidine tract)81 AATGGTGGCT CCATCTTAGC 9518
 H77CV-J6S
 H77(p7)CV-J6S (Polypyrimidine tract)81
 H77-J6S (Polypyrimidine tract)81
 H77(p7)-J6S (Polypyrimidine tract)81
 J6CF .AG..CGCA CAC.TTAG.. A.ACT.CA.A GCTAAC.G.. .C- (Polypyrimidine tract)132 ---

9519
 H77C CCTAGTCACG GCTAGCTGTG AAAGGTCCGT GAGCCGCATG ACTGCAGAGA GTGCTGATAC TGGCCTCTCT GCAGATCATG T 9599
 H77CV-J6S
 H77(p7)CV-J6S
 H77-J6S
 H77(p7)-J6S
 J6CFC.TA.. ...T.....

E2/p7/NS2 Region

730
 H77C RVCSCLMWMLLSQAEA ALENLVILNAASLAGTHGLVSFLVFFCFANWYLGKRWVPGAVYALYGMWPLLLALLPQRAYA LDTEVAASCGGVLVG 825
 H77CV-J6S ...A...LI.LG... ..K...H...A.SCN.FLY.VI..VA...I...V..L.T.S.T.L.SFS.....Q...
 H77(p7)CV-J6S ...A...LI.LG... ..K...H...A.SCN.FLY.VI..VA...I...V..L.T.S.T.L.SFS.....Q...
 H77-J6S ...A...LI.LG... ..K...H...A.SCN.FLY.VI..VA...I...V..L.T.S.T.L.SFS.....Q...
 H77(p7)-J6S ...A...LI.LG... ..K...H...A.SCN.FLY.VI..VA...I...V..L.T.S.T.L.SFS.....Q...
 J6CF ...A...LI.LG... ..K...H...A.SCN.FLY.VI..VA...I...V..L.T.S.T.L.SFS.....Q... Y.AS.HGQI.AAL..M



H77C

10	20	30	40	50	
1234567890	1234567890	1234567890	1234567890	1234567890	
GCCAGCCCC	TGATGGGGG	GACACTCCAC	CATGAATCAC	TCCCCGTGTA	50
GGAAC TACTG	TCTTCAACGA	GAAAGCGTCT	AGCCATGGGG	TTAGTATGAG	100
TGTCGTGCAG	CCTCCAGGAC	CCCCCTCC	GGGAGAGCCA	TAGTGGTCTG	150
CGGAACCGGT	GAGTACACCG	GAATTGCCAG	GACGACCGGG	TCCTTCTCTG	200
GATAAACCCG	CTCAATGCTT	GGAGATTTTGG	GGGTGCCCC	GCAAGACTGC	250
TAGCCGAGTA	GTGTGGGGT	GCGAAAGGCC	TTGTGGTACT	GGCTGATAGG	300
GTGCTTGCGA	GTGCCCCGGG	AGGTCCTGTG	GACCGTGCAC	CATGAGCAAG	350
AATCCTAAAC	CTCAAAGAAA	AACCAAACGT	AACAACAACC	GTCGCCACCA	400
GGACGTCAAG	TTCCCGGGTG	GGGTTCAGAT	CGTTGGTGGG	GTTTACTTGT	450
TGCCCGCGCAG	GGGCCCTAGA	TTGGGTGTGC	GGGGACGAG	GAAGACTTCC	500
GAGCGGTGCG	AACTCGAGG	TAGAAGTCAG	CCATATCCCA	AGGCACGTGG	550
GGCCGAGGGC	AGGACCTGGG	CTCAGCCCGG	GTACCCCTTG	CCCCCTCTATG	600
GCAATGAGGG	TTGCGGGTGG	GGGGATGGC	TCCTGTCTCC	CCGTGGCTCT	650
CGCCCTAGCT	GGGGCCCCAC	AGACCCCCCG	CGTAGGTGGC	GCAATTITGGG	700
TAAGGTCAATC	GATACCTTAA	CGTGGCGCTT	CGCCGACCTC	ATGGGGTACA	750
TACCGCTCGT	CGCGCCCCCT	CTTGGAGGGG	CTGCCAGGGC	CCTGGCGCAT	800
GGCGTCCGGG	TTCTGGAAGA	CGCGGTGAAC	TATGCAACAG	GGAACCTTCC	850
TGGTTGCTCT	TTCTCTATCT	TCCTTCTGGC	CCTGCTCTCT	TGCCCTGACTG	900
TGCCCCGCTTC	AGCCTACCAA	GTGCGCAATT	CCTCGGGGCT	TTACCATGTC	950
ACCAATGATT	GCCCTAAGTC	GAGTATTGTG	TACGAGGGGG	CCGATGCCAT	1000
CCTGCACACT	CCGGGGTGTG	TCCCTTGGGT	TGCGAGGGGT	AACGCCCTCGA	1050
GGTGTITGGGT	GGCGGTGACC	CCCACGGTGG	CCACCAGGGA	CGGCAAACTC	1100
CCCACAACGC	AGCTTCGACG	TCATATCGAT	CTGCTTGTGG	GGAGCGCCAC	1150
CCTCTGCTCG	GCCCTCTACG	TGGGGGACCT	GTGGGGGTCT	GTCTTCTCTG	1200
TTGGTCAACT	GTTTACCTTC	TCTCCAGGGC	GCCACTGGAC	GACGCAAGAC	1250
TGCAATTGTT	CTATCTATCC	CGGCATATA	ACGGGTATC	GCATGGCATG	1300
GGATATGATG	ATGAAGTGGT	CCCCTAAGGC	AGCGTTGGTG	GTAGCTCAGC	1350
TGCTCCGGAT	CCCACAAGCC	ATCATGGACA	TGATCGCTGG	TGCTCACTGG	1400
GGAGTCCCTGG	CGGGCATAGC	GTATTCTCTC	ATGGTGGGGA	ACTGGGGGAA	1450
GGTCCCTGGTA	GTGCTGCTGC	TATTTTGGCG	CGTGGACGGG	GAAACCCACG	1500
TCACCGGGGG	AAATGCCCGC	CGCACCAAGG	CTGGGCTTGT	TGGTCTCCTT	1550
ACACCAGGGG	CCAAGCAGAA	CATCCAAGTC	ATCAACAACA	ACGGCAGTTG	1600
GCACATCAAT	AGCACGGCCT	TGAATTGCAA	TGAAAGCCTT	AACACCGGCT	1650
GGTTAGCAGG	GCCTCTCTAT	CAACACAAAT	TCAACTCTTC	AGGCTGTCTT	1700
GAGAGGTTGG	CCAGCTGCCG	ACGCCTTACC	GATTTTGGCC	AGGGCTGGGG	1750
TCCTATCAGT	TATGCCAACG	GAAGCGGCTT	CGACGAAGCC	CCCTACTGCT	1800
GGCACTACCC	TCCAAGACCT	TGTGGCATTG	TGCCCCGAAA	GAGCGTGTTT	1850
GGCCCCGGTAT	ATTGCTTCAC	TCCCAGCCCC	GTGGTGGTGG	GAACGACCGA	1900

FIG. 6A

SUBSTITUTE SHEET (RULE 26)



H77C

10	20	30	40	50	
1234567890	1234567890	1234567890	1234567890	1234567890	
CAGGTCGGGC	GCGCCTACCT	ACAGCTGGGG	TGCAAATGAT	ACGGATGTCT	1950
TCGTCTTAA	CAACACCAGG	CCACCGCTGG	GCAATTGGTT	CGGTGTGACC	2000
TGGATGAACT	CAACTGGATT	CACCAAAGTG	TGCGGAGGCG	COOCTGTGT	2050
CATCGGAGGG	GTGGGCAACA	ACAOCITGCT	CTGCCCCACT	GATTGCTTCC	2100
GCAAACATCC	GGAAGCCACA	TACTCTGGGT	GCGGCTCCGG	TCCCTGGATT	2150
ACACCCAGGT	GCATGGTCCA	CTACCCGTAT	AGGCTTTGGC	ACTATCCTTG	2200
TACCATCAAT	TACACCATAT	TCAAAGTCAG	GATGTACGTG	GGAGGGGTGG	2250
AGCACAGGCT	GGAAGCGGCC	TGCAACTGGA	CGCGGGGCGA	ACGCTGTGAT	2300
CTGGAAGACA	GGGACAGGTC	CGAGCTCAGC	CGGTGTCTGC	TGTCCACCAC	2350
ACAGTGGCAG	GTCTTTCCGT	GTCTTTTCAC	GACCTGCGCA	GCTTGTGCGA	2400
CCGGCCTCAT	CCACCTCCAC	CAGAACATTG	TGGACGTGCA	GTAATTGTAC	2450
GGGGTAGGGT	CAAGCATGGC	GTCTTGGGCC	ATTAAGTGGG	AGTACGTGCT	2500
TCTCTGTGTC	CTTCTGCTTG	CAGACGCGCG	CGTCTGCTCC	TGCTTGTGGA	2550
TGATGTACT	CATATCCCAA	GCGGAGGCGG	CTTTGGAGAA	CCTCGTAATA	2600
CTCAATGCAG	CATCCCTGGC	CGGGACGCAC	GGTCTTGTGT	CCTTCTCTGT	2650
GTCTTCTGTC	TTTGGCGTGG	ATCTGAAGGG	TAGGTGGGTG	CCCGGAGCGG	2700
TCTACGCCCT	CTACGGGATG	TGGCCTCTCC	TCCCTGCTCC	GCTGGCGTTG	2750
CCTCAGCGGG	CATACGCACT	GGACACGGAG	GTGGCCGCGT	CGTGTGGCGG	2800
CGTTGTCTCT	GTCCGGTTAA	TGGCGCTGAC	TCTGTGCGCA	TATTACAAGC	2850
GCTATATCAG	CTGGTGCATG	TGGTGGCTTC	AGTATTTTCT	GACCAGAGTA	2900
GAAGCGCAAC	TGCACGTGTG	GGTCCCCCCC	CTCAACGTCC	GGGGGGGGCG	2950
CGATGCCGTC	ATCTTACTCA	TGTGTGTAGT	ACACCCGACC	CTGGTATTTG	3000
ACATCACCAA	ACTACTCCTG	GCCATCTTCG	GACCCCTTTG	GATTCTTCAA	3050
GCCAGTTTGC	TTAAAGTCCC	CTACTTGGTG	CGGTTTCAAG	GCTTCTCCCG	3100
GATCTGCGCG	CTAGCGCGGA	AGATAGCGGG	AGGTCAATTAC	GTGCAAATGG	3150
CCATCATCAA	GTTAGGGGGG	CTTACTGGCA	CCTATGTGTA	TAAOCATCTC	3200
ACCCCTCTTC	GAGACTGGGC	GCACAACGGC	CTGGGAGATC	TGGCGGTGGC	3250
TGTGGAACCA	GTGTCTTTCT	CCCGAATGGA	GACCAAGCTC	ATCAGTGGGG	3300
GGGCAGATAC	CGCCGCGTGC	GGTGACATCA	TCAACGGCTT	GCCCGTCTCT	3350
GCCCCGTAGG	GCCAGGAGAT	ACTGCTTGGG	CCAGCCGACG	GAATGGTCTC	3400
CAAGGGGTGG	AGGTGTCTGG	CGCCCATCAC	GCGTACGGCC	CAGCAGACGA	3450
GAGCCCTCCT	AGGGTGTATA	ATCACCAGCC	TGACTGGCCG	GGACAAAAC	3500
CAAGTGGAGG	GTGAGGTCCA	GATCGTGTCA	ACTGCTACCC	AAACCTTCTT	3550
GGCAACGTGC	ATCAATGGGG	TATGCTGGAC	TGCTTACCAC	GGGGCCGGAA	3600
CGAGGACCAT	CGCATCACCC	AAGGGTCTTG	TCATCCAGAT	GTATACCAAT	3650
GTGGACCAAG	ACCTTGTGGG	CTGGCCCGCT	CCTCAAGGTT	CCCGCTCATT	3700
GACACCCCTGT	ACCTGCGGCT	CCTGGACCTT	TTACCTGGTC	ACGAGGCACG	3750
CCGATGTCAT	TCCCGTGGCG	CGCGGAGGTG	ATAGCAGGGG	TAGCCTGCTT	3800

FIG. 6B

SUBSTITUTE SHEET (RULE 26)



H77C

10	20	30	40	50	
1234567890	1234567890	1234567890	1234567890	1234567890	
TGCCCCCGGC	CCATTTCCTA	CTTGAAAGGC	TCCTCGGGGG	GTCCGCTGTT	3850
GTGCCCCGCG	GGACACGGCG	TGGGCTTATT	CAGGGGCGCG	GTGTGCACCC	3900
GTGGAGTGGC	TAAAGCGGTG	GACTTTTATC	CTGTGGAGAA	CCTAGGGACA	3950
ACCATGAGAT	CCCGGTGTT	CACGGACAAC	TCCTCTCCAC	CAGCAGTGCC	4000
CCAGAGCTTC	CAGGTGGGCC	ACCTGCATGC	TCCCACGGGC	AGCGGTAAAG	4050
GCACCAAGGT	CCCGGCTGGG	TAAGCAGGCG	AGGGCTACAA	GGTGTGGTG	4100
CTCAACCCCT	CTGTGTGCTG	AACGCTGGGC	TTTGGTGCCT	ACATGTCCAA	4150
GGCCCATGGG	GTTGATCCCTA	ATATCAGGAC	CGGGGTGAGA	ACAATTACCA	4200
CTGGCAGGCC	CATCACGTAC	TCCACCTAAG	GCAAGTTCTT	TGCGAAGGC	4250
GGGTGCTCAG	GAGGTGCTTA	TGACATAATA	ATTTGTGAGG	AGTGCCACTC	4300
CACGGATGCC	ACATCCATCT	TGGGCATCGG	CAGTGTCTTT	GACCAAGCAG	4350
AGACTGGGGG	GGCGAGACTG	GTTGTGCTCG	CCACTGCTAC	CCCTCGGGGC	4400
TCCGTCACTG	TGTCCCATCC	TAACATCGAG	GAGGTGCTTC	TGTCCACCAC	4450
CGGAGAGATC	CCCTTTTACG	GCAAGGCTAT	CCCCCTCGAG	GTGATCAAGG	4500
GGGGAAGACA	TCTCATCTTC	TGCCACTCAA	AGAAGAAGTG	CGACGAGCTC	4550
GCCGCGAAGC	TGGTCCGATT	GGGCATCAAT	GCCGTGGCCT	ACTACCGCGG	4600
TCTTGACGTG	TCTGTICATC	CGACCAGCGG	CGATGTTGTC	GTGTTGTGGA	4650
CCGATGCTCT	CATGACTGGC	TTTACCGGGG	ACTTCGACTC	TGTGATAGAC	4700
TGCAACACGT	GTTGCACTCA	GACAGTCGAT	TTCAGCCTTG	ACCCTACCTT	4750
TACCATTTAG	ACAACCACGC	TCCCCCAGGA	TGCTGTCTCC	AGGACTCAAC	4800
GCCGGGGCAG	GACTGGCAGG	GGGAAGCCAG	GCATCTATAG	ATTTGTGGCA	4850
CCGGGGGAGC	GCCCCCTCCG	CATGTTCCGAC	TGTCGGTCC	TCTGTGAGTG	4900
CTATGACGGG	GGCTGTGCTT	GGTATGAGCT	CAGGCCCCGC	GAGACTACAG	4950
TTAGGCTACG	AGCGTACATG	AACACCCCGG	GGCTTCCCGT	GTGCCAGGAC	5000
CATCTTGAAT	TTTGGGAGGG	CGTCTTTAAG	GGCTCCTCTC	ATATAGATGC	5050
CCACTTTTAA	TCCAGACAA	AGCAGAGTGG	GGAGAAGTTT	OCTTACCTGG	5100
TAGCGTACCA	AGCCACGGTG	TGCGCTAGGG	CTCAAGGCCC	TCCCCCATCG	5150
TGGGACCAGA	TGTGGAAGTG	TTTGATCCGC	CTTAAACCCA	CCCTCCATGG	5200
GCCAACACCC	CTGCTATACA	GACTGGGGGC	TGTTGAGAAT	GAAGTCACCC	5250
TGACGCACCC	AATCACCAAA	TACATCATGA	CATGCATGTC	GCCGACCTTG	5300
GAGGTGCTCA	CGAGCACCTG	GGTCTCTGTT	GGGGGGTCC	TGGCTGCTCT	5350
GGCCGGGTAT	TGCTGTCAA	CAGGCTGGGT	GGTCATAGTG	GGCAGGATCG	5400
TCTTGTCCGG	GAAGCCGGCA	ATTATACCTG	ACAGGGAGGT	TCTCTACCAG	5450
GAGTTCGATG	AGATGGAAGA	GTCCTCTCAG	CACTTACCGT	ACATCGAGCA	5500
AGGGATGATG	CTCGCTGAGC	AGTTCAAGCA	GAAGGCCCTC	GGCCTCCTGC	5550
AGACCGGTC	CCGCCATGCA	GAGGTTATCA	CCCTGCTGT	CCAGACCAAC	5600
TGGCAGAAAC	TGAGGTCTTT	TTGGGCGAAG	CACATGTGGA	ATTTCATCAG	5650
TGGGATACAA	TACTTGGCGG	GCTGTCAAC	GCTGCCTGGT	AACCCCGCCA	5700

FIG. 6C

SUBSTITUTE SHEET (RULE 26)



H77C

10	20	30	40	50	
1234567890	1234567890	1234567890	1234567890	1234567890	
TTCCTTCATT	GATGGCTTTT	ACAGCTGCGG	TCACCAGCCC	ACTAACCCT	5750
GGCCAAACCC	TCCTCTTCAA	CATATTGGGG	GGGTGGGTGG	CTGCCCAGCT	5800
CGCCGCCCCC	GGTGCCGCTA	CTGCTTTTGT	GGGTGCTGGC	CTAGCTGGCG	5850
CCGCCATCGG	CAGCGTTGGA	CTGGGGAAGG	TCCTCGTGGA	CATTCTTGCA	5900
GGGTATGGCG	CGGGGCTGGC	GGGAGCTCTT	GTAGCATTC	AGATCATGAG	5950
CGGTGAGGTC	CCCTCCACGG	AGGACCTGGT	CAATCTGCTG	CCCGCCATCC	6000
TCTCGOCTGG	AGCCTTTGTA	GTCGGTGTGG	TCTGCGCAGC	AATACTGGCG	6050
CGGCACGTTG	GCCCCGGCGA	GGGGGCAGTG	CAATGGATGA	ACCGGCTAAT	6100
AGCCTTCGCC	TCCCGGGGGA	ACCATGTTTC	CCCCAGCAC	TACGTGCGG	6150
AGAGCGATGC	AGCCGCCCCG	GTCACGTGCA	TACTCAGCAG	CCTCACTGTA	6200
ACCCAGCTCC	TGAGGCGACT	GCATCAGTGG	ATAAGCTCGG	AGTGTACCC	6250
TCCATGCTCC	GGTTCCTGGC	TAAGGGACAT	CTGGGACTGG	ATATGCGAGG	6300
TGCTGAGCGA	CTTTAAGACC	TGGCTGAAAG	CCAAGCTCAT	GCCACAACCTG	6350
CCTGGGATTC	CCTTTGTGTC	CTGCCAGCGC	GGGTATAGGG	GGGTCTGGCG	6400
AGGAGACGGC	ATTATGCACA	CTCGCTGCCA	CTGTGGAGCT	GAGATCACTG	6900
GACATGTCAA	AAACGGGACG	ATGAGGATCG	TGGTTCCTAG	GACCTGCAGG	6950
AACATGTGGA	GTGGGACGTT	CCCCATTAAC	GCCTACACCA	CGGGCCCCCTG	6550
TACTCCCCCT	CCTGCGCCGA	ACTATAAGTT	CGCGCTGTGG	AGGGTGTCTG	6600
CAGAGGAATA	CGTGGAGATA	AGGCGGGTGG	GGGACTTCCA	CTACGTATCG	6650
GGTATGACTA	CTGACAATCT	TAAATGCCCC	TGCCAGATCC	CATCGCCCCGA	6700
ATTTTTTACA	GAATTGGACG	GGGTGCGCCT	ACACAGGTTT	GCGCCCCCTT	6750
GCAAGCCCTT	GCTGCGGGAG	GAGGTATCAT	TCAGAGTAGG	ACTCCACGAG	6800
TACCCGGTGG	GGTCCGAATT	ACCTTGCGAG	CCCGAACCGG	ACGTAGCCGT	6850
GTGACGTTCC	ATGCTCACTG	ATCCCTCCCA	TATAACAGCA	GAGGCGGCGG	6900
GGAGAAGGTT	GCGGAGAGGG	TCACCCCTTT	CTATGGCCAG	CTCCTGGGCT	6950
AGCCAGCTGT	CCGCTCCATC	TCTCAAGGCA	ACTTGCACCG	CCAACCATGA	7000
CTCCCTTGAC	GCCGAGCTCA	TAGAGGCTAA	CCTCCTGTGG	AGGCAGGAGA	7050
TGGGCGGCAA	CATCACCAGG	GTGAGTCAG	AGAACAAGT	GGTGATTCTG	7100
GACTCCTTCG	ATCCGCTTGT	GCGAGAGGAG	GATGAGCGGG	AGGCTCCCGT	7150
ACCTGCAGAA	ATTCTGCGGA	AGTCTCGGAG	ATTGCGCCCG	GCCCTGCCCC	7200
TCTGGGCGCG	GCCGACTTAC	AACCCCCCGC	TAGTAGAGAC	GTGGAAAAAG	7250
CCTGACTACG	AACCACCTGT	GGTCCATGGC	TGCCCCGTAC	CACCTCCACG	7300
GTCCCCCTCT	GTGCTCCGCG	CTCGGAAAAA	GCGTAAGGTG	GTCCTCACCG	7350
AATCAACCCCT	ATCTACTGCG	TTGGCCGAGC	TTGCCACCAA	AAGTTTGTGG	7400
AGCTCCTCAA	CTTCCGGCAT	TACGGGCGAC	AATAAGACAA	CATCCTCTGA	7450
GCCCCCCCCCT	TCTGGCTGCC	CCCCCGACTC	CGACGTTGAG	TCCTATTCTT	7500
CCATGCCCCC	CCTGGAGGGG	GAGCCTGGGG	ATCCGGATCT	CAGCGACGGG	7550
TCATGGTTCGA	CGGTCAGTAG	TGGGGCCGAC	ACCGAAGATG	TCGTGTGCTG	7600

FIG. 6D

SUBSTITUTE SHEET (RULE 26)



H77C

10	20	30	40	50	
1234567890	1234567890	1234567890	1234567890	1234567890	
CTCAATGTCT	TATTCCTGGA	CAGGCGCACT	CGTCACCCCG	TGCGCTGCGG	7650
AAGAACA AAA	ACTGCCCATC	AAGCCTCTGA	GCAACTCGTT	GCTAAGCCAT	7700
CACAATCTGG	TGTATTCCAC	CACTTACGCG	AGTGCTTGCC	AAAGGCAGAA	7750
GAAAGTCACA	TTTGACAGAC	TGCAAGTTCT	GGACAGCCAT	TACCAGGACG	7800
TGCTCAAGGA	GGTCAAAGCA	GCGGCGTCAA	AAGTGAAGGC	TAACTTGCTA	7850
TOCGTAGAGG	AAGCTTG CAG	CCTGAAGGCC	CCACATT CAG	CCAAATCCAA	7900
GTTTGGCTAT	GGGGCAAAG	ACGTCCGTTG	CCATCCCAGA	AAGGCGTAG	7950
CCCACATCAA	CTCCGTGTGG	AAAGACCTTC	TGGAAGACAG	TGTAACACCA	8000
ATAGACACTA	CCATCATGGC	CAAGAACGAG	GTTTCTCTCG	TTCAGCCTGA	8050
GAAGGGGGGT	CGTAAGCCAG	CTCGTCTCAT	CGTGTTCGCC	GACCTGGGCG	8100
TGCGCGTGTG	CGAGAAGATG	GCCCTGTACG	ACGTGGTTAG	CAAGCTCCCC	8150
CTGGCCGTGA	TGGGAAGCTC	CTACGGATT C	CAATACTCAC	CAGGACAGCG	8200
GGTTGAATTC	CTCGTGCAAG	CGTGG AAGTC	CAAGAAGACC	CCGATGGGGT	8250
TCTCGTATGA	TACCCGCTGT	TTTGACTCCA	CAGTCACTGA	GAGCGACATC	8300
CGTACGGAGG	AGGCAATTTA	CCAATGTTGT	GACCTGGACC	CCCAAGCCCG	8350
CGTGGCCATC	AAGTCCCTCA	CTGAGAGGCT	TTATGTTGGG	GGCCCTCTTA	8400
CCAATTCAAG	GGGGGAAAC	TGCGGCTACC	GCAGGTGCCG	CCGAGCGGC	8450
GTA CTGACAA	CTAGCTGTGG	TAACACCCCTC	ACTTGCTACA	TCAAGGCCCG	8500
GGCAGCCTGT	CGAGCCGCAG	GGCTCCAGGA	CTGCACCATG	CTCGTGTGTG	8550
GCGACGACTT	AGTCGTTATC	TGTGAAAGTG	CGGGGGTCCA	GGAGGACGCG	8600
GCGAGCCTGA	GAGCCTTCAC	GGAGGCTATG	ACCAGGTACT	CCGCCCCCCC	8650
CGGGGACCCC	CCACAACCAG	AATACGACTT	GGAGCTTATA	ACATCATGCT	8700
CCTCCAACGT	GTCAGTCGCC	CACGACGGCG	CTGGAAAGAG	GGTCTACTAC	8750
CTTACCCGTG	ACCCCTACAAC	CCCCCTCGCG	AGAGCCGCGT	GGGAGACAGC	8800
AAGACACACT	CCAGTCAATT	CCTGGCTAGG	CAACATAATC	ATGTTTGCCC	8850
CCACACTGTG	GGCGAGGATG	ATACTGATGA	CCCATTTCTT	TAGGTCTCTC	8900
ATAGCCAGGG	ATCAGCTTGA	ACAGGCTCTT	AACTGTGAGA	TCTAAGGAGC	8950
CTGCTACTCC	ATAGAACCAC	TGGATCTACC	TOCAATCATT	CAAAGACTCC	9000
ATGGCCTCAG	CGCATTTTCA	CTCCACAGTT	ACTCTCCAGG	TGAAATCAAT	9050
AGGGTGGCCG	CATGCCCTCAG	AAAACCTGGG	GTCCCGCCCT	TGCGAGCTTG	9100
GAGACACCGG	GCCCGGAGCG	TCCGCGCTAG	GCTTCTGTCC	AGAGGAGGCA	9150
GGGCTGCCAT	ATGTGGCAAG	TACCTCTTCA	ACTGGGCAGT	AAGAACA AAG	9200
CTCAA ACTCA	CTCCAATAGC	GGCCGCTGGC	CGGCTGGACT	TGTCCGGTTG	9250
GTTCA CGGCT	GGCTACAGCG	GGGGAGACAT	TTATCACAGC	GIGTCTCATG	9300
CCCGGCCCCG	CTGGTCTCTG	TTTTGCCCTAC	TCCTGCTCGC	TGCAGGGGTA	9350
GGCATCTACC	TCCTCCCCAA	CCGATGAAGG	TTGGGGTAAA	CACTCCGGCC	9400
TCTTAAGCCA	TTTCCGTGTT	TTTTTTTTTT	TTTTTTTTTT	TTTTTCTTTT	9450
TTTTTTTCTT	TCCTTTCCTT	CTTTTTTTC	TTTCTTTTTC	CCTTCTTTAA	9500

FIG. 6E

SUBSTITUTE SHEET (RULE 26)



H77C

10	20	30	40	50	
1234567890	1234567890	1234567890	1234567890	1234567890	
TGGTGGCTCC	ATCTTAGCCC	TAGTCACGGC	TAGCTGTGAA	AGGTCCGTGA	9550
GCCGCATGAC	TGCAGAGAGT	GCTGATACTG	GCTCTCTGTC	AGATCATGT	9599

FIG. 6F



H77C

10	20	30	40	50	
1234567890	1234567890	1234567890	1234567890	1234567890	
MSINPKPQRK	TKRNINRRPQ	DVKFPGGGQI	VGGVYLLPRR	GPRLGVRATR	50
KTSESRQPRG	RRQPIPKARR	PEGRIWAQPG	YFWPLYGNEG	CGWAGWLLSP	100
RGSRPSWGPT	DPRRRSRNLG	KVIDTLTOGF	ADLMGYIFLV	GAPLGGAARA	150
LAHGVRVLED	GVNYATGNLP	GCSFSIFLLA	LLSCLTVPAS	AYQVRNSSGL	200
YHVINDCHNS	SIVYEAADAI	LHTFGCVPCV	REGNASROW	AVTPTVATRD	250
GKLPITQLRR	HIDLLVGSAT	LCSALYVGDL	CGSVFLVGQL	FTFSPRRHWT	300
TQDQNCSTYP	GHTTGHMAW	DMMNWSPTA	ALVVAQLLRI	PQAIMDMTAG	350
AHWGVLAGIA	YFSMVGWAK	VLVVLILLFAG	VDAEIHVIGG	NAGRTTAGLV	400
GLLTFGAKQN	IQLININGSW	HINSTALNCH	ESLNTGWLAG	LFYQHKFNSS	450
GCPERLASCR	RLIDFAQGWG	PISYANGSGL	DERPYCWHYP	PRPOGIVPAK	500
SVCGPVYCFT	PSFVVGITD	RSGAPTYSWG	ANDIDVFLN	NIRPPLGNWF	550
GCIWMNSTGF	TKVCGAPPCV	IGGVGNNTLL	CPTDCFRKHP	EATYSRCGSG	600
FWITPRCVD	YPYRLWHYPC	TINYTIFKVR	MYVGGVEHRL	EAAQNWIRGE	650
RCDLEDRLRS	ELSPILLSTT	QWQVLPSCFT	TLPALSTGLI	HLHQNIVDVQ	700
YLYGVGSSIA	SWAIKWEYV	LLFLLLLADAR	VCSCILWMLL	ISQAEAALEN	750
LVIILNAASLA	GIHGLVSFLV	FFCFAWYLKG	RWVPGAVYAL	YGMWPLLLLL	800
LALPQRAYAL	DTEVAASCGG	VVLVGLMALT	LSPYYKRYIS	WOMWLLQYFL	850
TRVEAQLHW	VPPLNVRGGR	DAVILLMCVV	HPTLVFDITK	LLLAIFGFLW	900
ILQASLLKVP	YFVRVQGLLR	ICALARKIAG	GHYVQMAITK	LGALTGTIVY	950
NHLTPLRDWA	HNGLRDLAVA	VEPVVFSRME	TKLITWGADT	AACGDIINGL	1000
PVSARRQGEI	LLGPADGMVS	KGRLLAPIT	AYAQQTRGLL	GCIITSLTGR	1050
DKNQVEGEVQ	IVSTATQIFL	ATCINGVCWT	VYHGAGIRTI	ASPKGPVIQM	1100
YTNVDQDLVG	WPAPQGSRL	TPCTCGSSDL	YLVTRHADVI	PVRRRGDSRG	1150
SLLSPRPISY	LKGSSGGPLL	CPAGHAVGLF	RAAVCTRGVA	KAVDFTFVEN	1200
LGTIMRSPVF	TINSSPPAVP	QSFQVAHLHA	PTGSGKSTKV	PAAYAAQGYK	1250
VLVLNPSVAA	TLGFGAYMSK	AHGVDENIRT	GVRTITTTGSP	ITYSTYGFKL	1300
ADGGCSCGAY	DIICDECHS	TDATSLIGIG	TVLDQAETAG	ARLVVLATAT	1350
PPGSVTVSHP	NIEEVALSTT	GEIPFYGKAI	PLEVIKGRH	LIFCHSKKKC	1400
DELAACKLAL	GINAVAYYRG	LDVSVIPTSG	DVVVSTDAL	MIGFTGDFDS	1450
VIDCNICVTQ	TVDFSLDPTF	TIETTTILPQD	AVSRTQRRGR	TGRGKPGIYR	1500
FVAPGERPSG	MFDSSVLCEC	YDAGCAWYEL	TPAETTVRLR	AYMNTPLFV	1550
CQDHLEFWEG	VFTGLTHIDA	HFLSQIKQSG	ENFPYLVAYQ	ATVCARAQAP	1600
PPSWDQMWKC	LIRLKPTLHG	PTPLLYRLGA	VQNEVTLIHP	ITKYMTQMS	1650
ADLEVVTSTW	VLVGGVLAAL	AAYCLSTGCV	VTVGRIVLSG	KPAIIPDREV	1700
LYQEFDEMEE	CSQHLPHYEQ	GMLAEQFKQ	KALGLIQIAS	RHAEVITPAV	1750
QINWQKLEVF	WAKHMANFIS	GIQYLAGLST	LPGNPATASL	MAFTAAVTSP	1800
LTTGQITLLFN	ILGGWAAQL	AAPGAATAFV	GAGLAGAAIG	SVGLGKVLVD	1850
ILAGYGAGVA	GALVAFKIMS	GEVPSTEDLV	NLLPAILSPG	ALVVGWCAA	1900

FIG. 6G

SUBSTITUTE SHEET (RULE 26)



H77C

10	20	30	40	50	
1234567890	1234567890	1234567890	1234567890	1234567890	
ILRRHVGPGE	GAVQWMNRLI	AFASRGNHVS	PTHYVPESDA	AARVITAILSS	1950
LTVTQLLRRL	HQWISSECTT	PCSGSWLRDI	WDWICEVLSD	FKIWLKAKLM	2000
PQLPGIPFVS	CQRGYRGWVR	GDGIMHIRCH	CGAETTGHVK	NGIMRIVGPR	2050
TCRNWMSGTF	PINAYTTGPC	TPLPAPNYKF	ALWRVSAEEY	VEIRRVGDFH	2100
YVSGMTIDNL	KCPCQIPSPF	FFTELDGVRL	HRFAPPCKPL	LREEVSFRVG	2150
LHEYFVGSQI	PCEPEPDVAV	LTSMLTDPST	ITAEAAGRRL	ARGSPPSMAS	2200
SSASQLSAPS	LKATCTANHD	SPDAELIEAN	LLWRQEMGGN	ITRVESENKV	2250
VILDSFDPLV	AEEDEREVSF	PAETLRKSRR	FARALPWAR	PDYNPPLVET	2300
WKKPDYEPPV	VHGCPLPPPR	SPFVPPPRKK	RTVVLTESTL	STALAEIATK	2350
SFGSSSTSGI	TGDNITTSSE	PAPSGCPPDS	DVESYSSMPP	LEGEFGDPL	2400
SDGSWSTVSS	GADTEDVCC	SMSYSWIGAL	VTPCAAEEQK	LPINALSNL	2450
LRHNLVYST	TSRSACQROK	KVTFDRLQVL	DSHYQDLKE	VKAAASKVKA	2500
NLLSVEEACS	LTPPHSAKSK	FGYGAKDVRC	HARKAVAHIN	SVWKDILLED	2550
VTPIDTTIMA	KNEVFCVQPE	KGGRKPARLI	VFPDLGVRVC	EKMALYDVS	2600
KLPLAVMGSS	YGFQYSPGQR	VEFLVQAWKS	KKTPMGFSYD	TRCFDSIVTE	2650
SDIRTEEAIF	QCCDLDPQAR	VAIKSLTERL	YVGGPLTNSR	GENCGYRRCR	2700
ASGVLTTSCG	NILTCYIKAR	AACRAAGLQD	CIMLVCGDDL	VVICESAGVQ	2750
EDAASLRAFT	EAMTRYSAAP	GDPQPEYDL	ELITSCSSNV	SVAHDGAGKR	2800
VYYLTRDPTT	PLARAAWETA	RHTFVNSWL	NIIMFAPTLW	ARMILMIHFF	2850
SVLIARDQLE	QALNCETYGA	CYSIEPLDLP	PIIQRHLGLS	AFSLHSYSFG	2900
EINRVAACLR	KLGVPPLRAW	RHRARSVRAR	LLSRGGRAAI	CGKYLENWAV	2950
RTKLKLTPIA	AAGRDLDSGW	FTAGYSGDOI	YHSVSHARPR	WFWFCLLLLA	3000
AGVGTYLLFN	R				3011

FIG. 6H



HC-J4

10	20	30	40	50	
1234567890	1234567890	1234567890	1234567890	1234567890	
GCCAGCCCC	TGATGGGGC	GACACTCCAC	CATGAATCAC	TCCCCGTGGA	50
GGAACTACTG	TCTTCACGCA	GAAAGCGTCT	AGCCATGGCG	TTAGTATGAG	100
TGTCGTGCAG	CCTCCAGGAC	CCCCCTCC	GGGAGAGCCA	TAGTGGTCTG	150
CGGAACCGGT	GAGTACACCG	GAATTGCCAG	GACGACGGG	TCCTTTCTTG	200
GATCAACCCG	CTCAATGCCT	GGAGATTTGG	GCGTGCCCC	GCGAGACTGC	250
TAGCCGAGTA	GTGTGTGGGTC	GCGAAAGGCC	TTGTGGTACT	GCCTGATAGG	300
GTGCTTGCGA	GTGCCCCGGG	AGGTCTCGTA	GACCGTGCAC	CATGAGCACG	350
AATCCTAAAC	CTCAAAGAAA	AACCAAACGT	AACACCAACC	GCCGCCACA	400
GGACGTCAAG	TTCCCCGGCG	GTGGTCAGAT	CGTTGGTGA	GTATACCTGT	450
TGCCGCGCAG	GGGCCCCAGG	TTGGGTGTGC	GCGGACTAG	GAAGGCTTCC	500
GAGCGGTCCG	AACCTCGTGG	AAGGCGACAA	CCTATCCCAA	AGGCTCGCCG	550
ACCCGAGGGC	AGGGCCTGGG	CTCAGCCCCG	GTACCCCTTG	CCCCCTATG	600
GCAATGAGGG	CCTGGGGTGG	GCAGGATGGC	TCCGTGCACC	CCGGGCTCC	650
CGGCTTAGTT	GGGGCCCCAC	GGACCCCCG	CGTAGGTCCG	GTAACTTGGG	700
TAAGGTATC	GATACCCCTA	CATGCGGCTT	CGCCGATCTC	ATGGGGTACA	750
TTCCGCTCGT	CGGCGCCCC	CTAGGGGGCG	CTGCCAGGGC	CTTGGCACAC	800
GGTGTCCGGG	TTCTGGAGGA	CGGCGTGAAC	TATGCAACAG	GGAACTTGCC	850
CGGTGTCTCT	TTCTCTATCT	TCCTCTTGGC	TCTGCTGTCC	TGTTTGACCA	900
TCCCAGCTTC	CGCTTATGAA	GTGCGCAACG	TGTCCGGGAT	ATACCATGTC	950
ACGAACGACT	GCTCCAACCTC	AAGCATTTGTG	TATGAGGCAG	CGGACGTGAT	1000
CATGCATACT	CCCGGGTGG	TGCCCTGTGT	TCAGGAGGGT	AACAGCTCCC	1050
GTGTCTGGGT	AGCGCTCACT	CCCACGCTCG	CGGCCAGGAA	TGCCAGCGTC	1100
CCCACTACGA	CAATACGACG	CCACGTGCAC	TTGCTCGTTG	GGACGGCTGC	1150
TTTCTGCTCC	GCTATGTACG	TGGGGGATCT	CTGCCGATCT	ATTTTCCTCG	1200
TCTCCAGCT	GTTCACCTTC	TGCGCTCGCC	GGCATGAGAC	AGTGCAGGAC	1250
TGCAACTGCT	CAATCTATCC	CGGCCATGTA	TCAGGTACCC	GCAATGGCTTG	1300
GGATATGATG	ATGAACTGGT	CACCTACAAC	AGCCCTAGTG	GTGTGCGAGT	1350
TGCTCCGGAT	CCCACAAGCT	GTGTTGGACA	TGGTGGGGG	GGCCCACTGG	1400
GGAGTCCCTGG	CGGGCCCTTG	CTACTATTCC	ATGGTAGGGA	ACTGGGCTAA	1450
GGTTCTGATT	GTGGCGCTAC	TCTTTGCCGG	CGTTGACGGG	GAGAACCCACA	1500
CGACGGGGAG	GGTGGCCGGC	CACACCACT	CCGGGTTTAC	GTCCCTTTTC	1550
TCATCTGGGG	CGTCTCAGAA	AATCCAGCTT	GTGAATACCA	ACGGCAGCTG	1600
GCACATCAAC	AGGACTGCC	TAAATTGCAA	TGACTCCCTC	CAAACTGGGT	1650
TCTTTGCCGC	GCTGTTTAC	GCACACAAGT	TCAACTCGTC	CGGGTGCCCG	1700
GAGCGCATGG	CCAGCTGCCG	CCCCATTGAC	TGGTTCGCC	AGGGGTGGGG	1750
CCCCATCACC	TATACTAAGC	CTAACAGCTC	GGATCAGAGG	CCTTATTGCT	1800
GGCATTAAGC	GCCTCGACCG	TGTGGTGTGC	TACCCGGGTC	GCAGGTGTGT	1850
GGTCCAGTGT	ATTGTTTCAC	CCCAAGCCCT	GTGTGGTGG	GGACCACCGA	1900

FIG. 7A

SUBSTITUTE SHEET (RULE 26)



HC-J4

10	20	30	40	50	
1234567890	1234567890	1234567890	1234567890	1234567890	
TCGTTCCGGT	GTCCCTACGT	ATAGCTGGGG	GGAGAATGAG	ACAGACGTGA	1950
TGCTCCTCAA	CAACACGGGT	CCGCCACAAG	GCAACTGGTT	CGGCTGTACA	2000
TGGATGAATA	GTACTGGGTT	CACTAAGACG	TGCGGAGGTC	CCCGGTGTAA	2050
CATCGGGGGG	GTCCGTAAAC	GCACCTTGAT	CTGCCCCACG	GACTGCTTCC	2100
GGAAGCACCC	CGAGGCTACT	TACACAAAAT	GTGGCTGGGG	GOOCTGGTTG	2150
ACACCTAGGT	GCCTAGTAGA	CTACCCATAC	AGGCTTTTGG	ACTACCCCTG	2200
CACCTCTCAAT	TTTTCCATCT	TTAAGGTTAG	GATGTATGTG	GGGGGGGTGG	2250
AGCACAGGCT	CAATGCCGCA	TGCAATTGGA	CTCGAGGAGA	GCGCTGTAAAC	2300
TTGGAGGACA	GGGATAGGTC	AGAACTCAGC	COGCTGCTGC	TGTCTACAAC	2350
AGAGTGGCAG	ATACTGCCCT	GTGCTTTTCAC	CACCCTAACG	GCTTTATCCA	2400
CTGGTTTGAT	CCATCTCCAT	CAGAACATCG	TGGACGTGCA	ATACCTGTAC	2450
GGTGTAGGGT	CAGCGTTTGT	CTCCTTTTGA	ATCAAATGGG	AGTACATCCT	2500
GTGTCTTTTC	CTTCTCCTGG	CAGACGGCGG	CGTGTGTGCC	TGCTTGTGGA	2550
TGATGCTGCT	GATAGCCCAG	GCTGAGGCCG	CCTTAGAGAA	CTTGGTGGTC	2600
CTCAATGCCG	CGTCCGTGGC	CGGAGCGCAT	GGTATTCTCT	CCTTTCTTGT	2650
GTCTTTCTGC	GCCGCCGTGG	ACATTAAAGG	CAGGCTGGCT	CTTGGGGGGG	2700
CGTATGCTTT	TTATGGCGTA	TGGCCGCTGC	TCCTGCTCCT	ACTGGCGTTA	2750
CCACCACGAG	CTTACGCCCT	GGACCGGGAG	ATGGCTGCAT	CGTGGGGGGG	2800
TGCGGTTCCT	GTAGGTCTGG	TATTCCTTGAC	CTTGTCACCA	TACTACAAAG	2850
TGTTTCTCAC	TAGGCTCATA	TGGTGGTTAC	AATACTTTAT	CACCAGAGCC	2900
GAGGCGCACA	TGCAAGTGTG	GGTCCCCCCC	CTCAACGTTT	GGGGAGGCCG	2950
CGATGCCATC	ATCCTCCTCA	CGTGTGCGGT	TCATCCAGAG	TTAATTTTTG	3000
ACATCACCAA	ACTCCTGCTC	GCCATACTCG	GCCCGCTCAT	GGTGCTCCAG	3050
GCTGGCATAA	CGAGAGTGCC	GTACTTCTGT	CGCGCTCAAG	GGCTCATTCG	3100
TGCATGCATG	TTAGTGCGAA	AAGTCGCCGG	GGGTCAATTAT	GTCCAAATGG	3150
TCTTCATGAA	GCTGGGCGCG	CTGACAGGTA	CGTACGTTTA	TAACCATCTT	3200
ACCCCACTGC	GGGACTGGGC	CCACGCGGGC	CTACGAGACC	TTGCGGTGGC	3250
GGTAGAGCCC	GTGCTCTTCT	CCGCCATGGA	GACCAAGGTC	ATCACTGGG	3300
GAGCAGACAC	CGCTGCGTGT	GGGGACATCA	TCTTGGGTCT	ACCGTCTCC	3350
GCCCGAAGGG	GGAAGGAGAT	ATTTTGTGGG	CCGGCTGATA	GTCTCGAAGG	3400
GCAAGGGTGG	CGACTCCTTG	CGCCCATCAC	GGCCTACTCC	CAACAAACGC	3450
GGGGCGTACT	TGGTTGCATC	ATCACTAGCC	TCACAGGCGG	GGACAAGAAC	3500
CAGGTGGAAG	GGGAGGTTCA	AGTGGTTTCT	ACCGCAACAC	AATCTTTCTT	3550
GGCGACCTGC	ATCAACGGCG	TGTGCTGGAC	TGTCTACCAT	GGCGCTGGCT	3600
CGAAGACCCT	AGCCGGTCCA	AAAGGTCCAA	TCACCCAAAT	GTACACCAAT	3650
GTAGACCTGG	ACCTCGTCCG	CTGGCAGGCG	CCCCCGGGG	CGCGCTCCAT	3700
GACACCATGC	AGCTGTGGCA	GCTCGGACCT	TTACTTGGTC	ACGAGACATG	3750
CTGATGTCAT	TCCGGTGCGC	CGGCGAGGCG	ACAGCAGGGG	AAGTCTACTC	3800

FIG. 7B

SUBSTITUTE SHEET (RULE 26)



HC-J4

10	20	30	40	50	
1234567890	1234567890	1234567890	1234567890	1234567890	
TCCCCCAGGC	CCGTCTCTTA	CCTGAAAGGC	TOCTCGGGTG	GTCCATTGCT	3850
TTGCCCCITCG	GGGCAAGTGG	TGGGGGTCTT	COGGGCTGCT	GTGTGCAACC	3900
GGGGGGTGGC	GAAGGCGGTG	GACTTCATAC	COGTTGAGTC	TATGGAAACT	3950
ACCATGCGGT	CTCCGGTCTT	CACAGACAAC	TCAACCCCCC	CGGCTGTACC	4000
GCAGACATTC	CAAGTGGCAC	ATCTGCAAGC	TOCTACTGGC	AGCGGCAAGA	4050
GCACCAAAGT	GCCGGCTGGG	TATGCAGCCC	AAGGGTACAA	GGTGCTGGTC	4100
CTGAACCCGT	COGTTGCGGC	CAOCTTAGGG	TTTGGGGGGT	ATATGTCCAA	4150
GGCACACGGT	ATCGACCCTA	ACATCAGAAC	TGGGGTAAAG	ACCATTACCA	4200
CGGGCGGCTC	CATTAGGTAC	TCCACCTATG	GCAAGTTCTT	TGCGGACGGT	4250
GGCTGTCTTG	GGGGCGCCTA	TGACATCATA	ATATGTGATG	AGTGCCACTC	4300
AAC TGACTCG	ACTACCATCT	TGGGCATGGG	CACAGTCTTG	GACCAAGGGG	4350
AGACGGCTGG	AGCGCGGCTC	GTCGTGCTCG	CCACCGCTAC	AOCTCCGGGA	4400
TGGTTTACCG	TGCCACACCC	CAATATCGAG	GAAATAGGCC	TGTCCAACAA	4450
TGGAGAGATC	CCCTTCTATG	GCAAAGOCAT	CCOCATTGAG	GCCATCAAGG	4500
GGGGGAGGCA	TCTCATTTTC	TGCCATTCCA	AGAAGAAATG	TGACGAGCTC	4550
GCCGCAAAGC	TGACAGGCCT	CGGACTGAAC	GCTGTAGCAT	ATTACCGGGG	4600
CCTTGATGTG	TCCGTCTATC	CGCCTATCGG	AGACGTCTGT	GTCGTGGCAA	4650
CAGACGCTCT	AATGACGGGT	TTCACCGGGG	ATTTTGACTC	AGTGATCGAC	4700
TGCAATACAT	GTGTACCCA	GACAGTCGAC	TTCAGCTTGG	ATCCCACCTT	4750
CACCATTGAG	ACGACGACCG	TGCCCCAAGA	CGCGGTGTGG	CGCTCGCAAC	4800
GGCGAGGTAG	AACTGGCAGG	GGTAGGAGTG	GCATCTACAG	GTTTGTGACT	4850
CCAGGAGAAC	GGCCCTCGGG	CATGTTTCGAT	TCTTCGGTCC	TGTGTGAGTG	4900
CTATGACCGG	GGCTGTGCTT	GGTATGAGCT	CACGCCCGCT	GAGACCTCGG	4950
TTAGGTTGCG	GGCTTACCTA	AATACACCAG	GGTTGCCCCG	CTGCCAGGAC	5000
CATCTGGAGT	TCTGGGAGAG	CGTCTTCACA	GGCCTCACCC	ACATAGATGC	5050
CCACTTCCTG	TCCAGACTA	AACAGGCAGG	AGACAACCTT	CCTTACCTGG	5100
TGGCATATCA	AGCTACAGTG	TGCGCCAGGG	CTCAAGCTCC	ACCTCCATCG	5150
TGGGACCAAA	TGTGGAAAGTG	TCTCATACGG	CTGAAACCTA	CACTGCACGG	5200
GCCAACACCC	CTGCTGTATA	GGCTAGGAGC	CGTCCAAAAT	GAGGTTCATCC	5250
TCACACACCC	CATAACTAAA	TACATCATGG	CATGCATGTC	GGCTGACCTG	5300
GAGGTCTGTA	CTAGCACCTG	GGTGCTGGTA	GGCGGAGTCC	TTCAGCTTTT	5350
GGCCGCATAC	TGCTTGACGA	CAGGCAGTGT	GGTCATTGTG	GGCAGGATCA	5400
TCTTGTTCCGG	GAAGCCAGCT	GTCGTTCCCG	ACAGGGAGGT	CCTCTACCAG	5450
GAGTTCGATG	AGATGGAAGA	GTGTGCCTCA	CAACTTCCTT	ACATCGAGCA	5500
GGGAATGCAG	CTCGCCGAGC	AATTCAAGCA	AAAGGCGCTC	GGGTGTGTTG	5550
AAACGGCCAC	CAAGCAAGCG	GAGGCTGCTG	CTCCCGTGGT	GGAGTCCAAG	5600
TGGCGAGCCC	TTGAGACCTT	CTGGGCGAAG	CACATGTGGA	ATTTTCATCAG	5650
CGGAATACAG	TACCTAGCAG	GCTTATCCAC	TCTGCCTGGA	AACCCCGCGA	5700

FIG. 7C

SUBSTITUTE SHEET (RULE 26)



HC-J4

10	20	30	40	50	
1234567890	1234567890	1234567890	1234567890	1234567890	
TAGCATCATT	GATGGCATT	ACAGCTTCTA	TCACTAGCCC	GCTCACCACC	5750
CAAAACACCC	TCCTGTTTAA	CATCTTGGGG	GGATGGGIGG	CTGCCCCAACT	5800
CGCTCCTCCC	AGCGCTGCGT	CAGCTTTTGT	GGGCGCCGGC	ATCGCCGGAG	5850
CGGCTGTGG	CAGCATAGGC	CTTGGGAAGG	TGCTGTGGGA	CATCTTGGCG	5900
GGCTATGGGG	CAGGGGTAGC	CGGCGCACTC	GTTGGCTTTA	AGGTCATGAG	5950
CGGCGAGGTG	CCCTCCACCG	AGGACCTGGT	CAACTTACTC	CCTGCCATCC	6000
TCTCTCCTGG	TGCCCTGGTC	GTCGGGGTGG	TGTGGGCAGC	AATACTGGGT	6050
CGGCACGTGG	GCCCGGGAGA	GGGGGCTGTG	CAGTGGATGA	ACCGGCTGAT	6100
AGCGTTGGCT	TGCGGGGGTA	ACCAAGTCTC	CCCTAAGCAC	TATGTGCCGT	6150
AGAGCGACGC	TGCAGCACGT	GTCACTCAGA	TCCTCTCTAG	CCTTAACATC	6200
ACTCAACTGC	TGAAGGGGCT	CCACCAGTGG	ATTAAATGAGG	ACTGCTCTAC	6250
GCCATGCTCC	GGCTCGTGGC	TAAGGGATGT	TTGGGATTGG	ATATGCAAGG	6300
TGTTGACTGA	CTTCAAGACC	TGGCTCCAGT	CCAAACTCCT	GCCGCGGTTA	6350
CCGGGAGTCC	CTTTCTCTGT	ATGCCAACGC	GGGTACAAGG	GAGTCTGGCG	6400
GGGGGACGGC	ATCATGCAAA	CCACCTGCCC	ATGCGGAGCA	CAGATCGCCG	6450
GACATGTCAA	AAACGGTTCC	ATGAGGATCG	TAGGGCCTAG	AACCTGCAGC	6500
AACACGTGGC	ACCGAAGGTT	CCCCATCAAC	GCATACACCA	CGGGACCTTG	6550
CACACCCCTC	CCGGCGCCCA	ACTATTCCAG	GGCGCTATGG	CGGGTGGCTG	6600
CTGAGGAGTA	CGTGGAGGTT	ACCGGTGTGG	GGGATTTCOA	CTAAGTGACG	6650
GGCATGACCA	CTGACAACGT	AAAGTGGCCA	TGCCAGGTTC	CGGCCCCCGA	6700
ATTCTTTCACG	GAGGTGGATG	GAGTGGCGTT	GCACAGGTAC	GCTCCGGCGT	6750
GCAAACCTCT	TCTACGGGAG	GACGTACAGT	TCCAGGTGGG	GCTCAACCAA	6800
TACTTGGTCC	GGTCGCAGCT	CCCATGCGAG	CCCGAACCGG	ACGTAAACAGT	6850
GCTTACTTCC	ATGCTCACCG	ATCCCTCCCA	CATTACAGCA	GAGACGGCTA	6900
AGCGTAGGCT	GGCTAGAGGG	TCTCCCCCCT	CTTTAGCCAG	CTCATCAGCT	6950
AGCCAGTTGT	CTGCGCCTTC	TTTGAAGGCG	ACATGCACTA	CCACCATGA	7000
CTCCCCGGAC	GCTGACCTCA	TCGAGGCCAA	CCTCTTGTGG	CGGCAGGAGA	7050
TGGGCGGAAA	CATCACTGGC	GTGGAGTCA	AGAATAAGGT	AGTAATTCTG	7100
GACTCTTTCC	AACCGCTTCA	CGCGGAGGGG	GATGAGAGGG	AGATATCCGT	7150
CGCGGCGGAG	ATCCTGCGAA	AATCCAGGAA	GTTCCCCCTA	GCGTTGCCCA	7200
TATGGGCACG	CCCGGACTAC	AATCCTCCAC	TGCTAGAGTC	CTGGAAGGAC	7250
CCGGACTACG	TCCCTCCGGT	GGTACACGGA	TGCCCATTGC	CACCTACCAA	7300
GGCTCCTCCA	ATACCACCTC	CACGGAGAAA	GAGGACGGTT	GTCCIGACAG	7350
AATCCAATGT	GTCTTCTGCC	TTGGCGGAGC	TGCCCACTAA	GACCTTCGGT	7400
AGCTCCGGAT	CGTCGGCCGT	TGATAGCGGC	ACGGCGACCG	CCCTTCCTGA	7450
CCTGGCCTCC	GACGACGGTG	ACAAAGGATC	CGACGTTGAG	TCGTACTCCT	7500
CCATGCCCCC	CCTTGAAGGG	GAGCCGGGGG	ACCCCGATCT	CAGCGACGGG	7550
TCTTGGTCTA	CCGTGAGTGA	GGAGGCTAGT	GAGGATGTGG	TCTGCTGCTC	7600

FIG. 7D

SUBSTITUTE SHEET (RULE 26)



HC-J4

10	20	30	40	50	
1234567890	1234567890	1234567890	1234567890	1234567890	
AATGTCCTAT	ACGTGGACAG	GCGCCCTGAT	CACGCCATGC	GCTGCGGAGG	7650
AAAGTAAGCT	GCCCATCAAC	COGTTGAGCA	ACTCTTTGCT	GCGTCACCAC	7700
AACATGGTCT	ACGCCACAAC	ATCCCGCAGC	GCAAGCCTCC	GGCAGAAGAA	7750
GGTCACCTTT	GACAGATTGC	AAGTCTGGA	TGATCATTAC	CGGGACGTAC	7800
TCAAGGAGAT	GAAGGCGAAG	GCGTCCACAG	TTAAGGCTAA	GCTTCTATCT	7850
ATAGAGGAGG	CCTGCAAGCT	GACGCCCCCA	CATTGGGCGA	AATCCAAATT	7900
TGGCTATGGG	GCAAAGGACG	TCCGGAACCT	ATCCAGCAGG	GOOGTTAACC	7950
ACATCCGCTC	CGTGTGGGAG	GACTTGCTGG	AAGACACTGA	AACACCAATT	8000
GACACCACCA	TCATGGCAAA	AAGTGAGGTT	TTCTGCGTCC	AACCAGAGAA	8050
GGGAGGCGGC	AAGCCAGCTC	GCCTTATCGT	ATTCCACAGC	CTGGGAGTTC	8100
GTGTATGCGA	GAAGATGGCC	CTTTACGACG	TGGTCTCCAC	CCTTCCTCAG	8150
GCCGTGATGG	GCTCCTCATA	CGGATTTCAA	TACTCCCCCA	AGCAGCGGGT	8200
CGAGTTCCTG	GTGAATACCT	GGAAATCAAA	GAAATGCOCT	ATGGGCTTCT	8250
CATATGACAC	CCGCTGTTTT	GACTCAACGG	TCACTGAGAG	TGACATTGGT	8300
GTTGAGGAGT	CAATTTACCA	ATGTTGIGAC	TTGGCCCCCG	AGGCCAGACA	8350
GGCCATAAGG	TGCTCACAG	AGCGGCTTTA	CATCGGGGGT	CCCCTGACTA	8400
ACTCAAAGG	GCAGAACTGC	GGTTATCGCC	GGTGCCGCGC	AAGTGGCGTG	8450
CTGACGACTA	GCTGCGGTAA	TACCCCTACA	TGTTACTTGA	AGGCCACTGC	8500
AGCCTGTGCA	GCTGCAAAGC	TCCAGGACTG	CACGATGCTC	GTGAACGGAG	8550
ACGACCTTGT	CGTTATCTGT	GAAAGCGCGG	GAACCCAGGA	GGATGCGGCG	8600
GCCCTACGAG	CCTTCACGGA	GGCTATGACT	AGGTAATCCG	CCCCCCCCCG	8650
GGATCCGCCC	CAACCAGAAT	ACGACCTGGA	GCTGATAACA	TCATGTTCTT	8700
CCAATGTGTC	AGTCGCGCAC	GATGCATCTG	GCAAAAGGGT	ATACTACCTC	8750
ACCCGTGACC	CCACCACCCC	CCTTGACCGG	GCTGCGTGGG	AGACAGCTAG	8800
ACACACTCCA	ATCAACTCTT	GGCTAGGCAA	TATCATCATG	TATGCGCCCA	8850
CCCTATGGGC	AAGGATGATT	CTGATGACTC	ACTTTTCTTC	CATCCTTCTA	8900
GCTCAAGAGC	AACTTGAAAA	AGCCCTGGAT	TGTCAGATCT	ACGGGGCTTG	8950
CTACTCCATT	GAGCCACTTG	ACCTACCTCA	GATCATTGAA	CGACTCCATG	9000
GTCTTAGCGC	ATTTACACTC	CACAGTTACT	CTCCAGGTGA	GATCAATAGG	9050
GTGGCTTCAT	GCCTCAGGAA	ACTTGGGGTA	CCACCTTGCC	GAACCTGGAG	9100
ACATCGGGCC	AGAAGTGTCC	GCGCTAAGCT	ACTGTCCACG	GGGGGGAGGG	9150
CCGCCACTTG	TGGCAGATAC	CTCTTTAACT	GGGCAGTAAG	GACCAAGCTT	9200
AAACTCACTC	CAATCCCGGC	CGCGTCCAG	CTGGACTTGT	CTGGCTGGTT	9250
CGTGGCTGGT	TACAGCGGGG	GAGACATATA	TCACAGCCTG	TCTCGTGCCC	9300
GACCCCGCTG	GTTCGGGTG	TGCTACTTCC	TACTTTCTGT	AGGGGTAGGC	9350
ATTTACCTGC	TCCCCAACCG	ATGAACGGGG	AGCTAACCCAC	TCCAGGCCTT	9400
AAGCCATTTT	CTGTTTTTTT	TTTTTTTTTT	TTTTTTTTTT	TCTTTTTTTT	9450
TTTCTTTCCT	TTCTTCTTT	TTTCTCTTC	TTTTTCCCTT	CTTTAATGGT	9500

FIG. 7E

SUBSTITUTE SHEET (RULE 26)



10	20	30	40	50	
1234567890	1234567890	1234567890	1234567890	1234567890	
GGCTCCATCT	TAGCCCTAGT	CACGGCTAGC	TGTGAAAGGT	CCGTGAGCCG	9550
CATGACTGCA	GAGAGTGCTG	ATACTGGCCT	CTCTGCAGAT	CATGT	9595

FIG. 7F



10	20	30	40	50	
1234567890	1234567890	1234567890	1234567890	1234567890	
MSINPKPQPK	TKRNINRRPQ	DVKFPGGGQI	VGGVYLLPRR	GPRLGVRATR	50
KASERSQPRG	RRQPIPKARR	PEGRAWAQFG	YFWPLYGNEG	LGWAGWLLSP	100
RGSRPSWGPT	DPRRRSRNLG	KVIDILITCGF	ADLMGYIPLV	GAPLGGAARA	150
LAHGVRVLED	GVNYATGNLP	GCSFSIFLLA	LLSCLTIPAS	AYEVRNVSGI	200
YHVINDCSNS	SIVYEADVI	MHTPGCVPCV	QEGNSSROW	ALITPILAARN	250
ASVPTTTIRR	HVDLLVGTA	FCSAMYVGD	CGSIFLVSQL	FTFSPPRHET	300
VQDCNCSTYP	GHSVGHMAW	IMMNWSPTT	ALVVSQLLRI	PQAVVDMVAG	350
AHWGLVLAGL	YYSWGVNWK	VLIVALLFAG	VDGEIHTTGR	VAGHITSGFT	400
SLFSSGASQK	IQLVNINGSW	HINRTALN	DSLQIGFFAA	LFYAHKFESS	450
GCPERMASCR	PIDWFAQGWG	PITYTKENSS	DQRPYOWHYA	PRPGVVPAS	500
QVCGPVYCF	PSPVVGTID	RSGVPTYSWG	ENETDMLLN	NIRPPQGNWF	550
GCTWMNSTGF	TKTCGGPPCN	IGGVGNRILI	CPIDCFRKHP	EATYIKOGSG	600
PWLTPRCLVD	YPYRLWHYPC	TINFSIFKVR	MYVGGVEHRL	NAACNWIRGE	650
RONLEDNRDS	ELSPLLLSTT	EWQILPCAFT	TLPALSTGLI	HLHQNIVDVQ	700
YLYGVGSAFV	SFAIKWEYIL	LLFLLLADAR	VCACIWMMLL	IAQAEAALEN	750
LWVLNAASVA	GAHGILSFLV	FFCAAWYIKG	RLAPGAAYAF	YGVWPLLLLL	800
LALPPRAYAL	DREMAASCGG	AVLVGLVFLT	LSPYYKVFLT	RLIWWLQYFI	850
TRAEAHMQW	VPPLNVRGGR	DAIILLTCAV	HPELIFDITK	LLAILGLPLM	900
VLQAGITRVP	YFVRAQGLIR	ACMLVRKVAG	GHYVQMVFMK	LGALITGYVY	950
NHLTPLRDWA	HAGLRDLAVA	VEPVVFSAME	TKVTIWGADT	AACGDIILGL	1000
PVSARRGKEI	FLGPADSLEG	QGWLLAPIT	AYSQQIRGVL	GCIITSLTGR	1050
DKNQVEGEVQ	VVSTATQSFL	ATCINGVCWT	VYHGAGSKTL	AGPKGPITQM	1100
YTINVDLDLVG	WQAPPGARSM	TPCSCGSSDL	YLVIRHADVI	PVRRRGDSRG	1150
SLSPRPVSY	LKGSSGGPLL	CPSGHVGVF	RAAVCIRGVA	KAVDFIPVES	1200
METIMRSPVF	TINSTPPAVP	QTFQVAHLHA	PTGSGKSTKV	PAAYAAQGYK	1250
VLVLNPSVAA	TLGFGAYMSK	AHGIDPNIRT	GVRTITITGGS	ITYSTYGFLL	1300
ADGGCSCGAY	DIICDECHS	TDSTTILGIG	TVLDQAETAG	ARLVLATAT	1350
PPGSVIVPHP	NIEEIGLSNN	GEIPFYGKAI	PTEAIKGRH	LIFCHSKKCC	1400
DELAACKLTGL	GLNAVAYYRG	LDVSVIPPIG	DVVVATDAL	MIGFTGDFDS	1450
VIDCNTCVIQ	TVDFSLDPTF	TIETTTVPQD	AVSRSQRRGR	TGRGRSGIYR	1500
FVTPGERPSG	MFDSSVLCEC	YDAGCAWYEL	TPAETSVRLR	AYLNTFGLPV	1550
CQDHLEFWES	VFTGLTHIDA	HFLSQIKQAG	DNFPYLVAYQ	ATVCARAQAP	1600
PPSWDQWAKC	LIRLKPTLHG	PTFLLYRLGA	VQNEVILTHP	ITKYIMACMS	1650
ADLEVVTSTW	VLVGGVLAAL	AAYCLTTGSV	VIVGRIILSG	KPAVVPDREV	1700
LYQEFDEMEE	CASQLPYIEQ	GMQLAEQFKQ	KALGLLQTAT	KQAEAAAPVV	1750
ESKWRALETF	WAKHMANFIS	GIQYLAGLST	LPGNPATIASL	MAFTASITSP	1800
LTTQNTILLEN	ILGGWAAQL	APPSAASAFV	GAGIAGAAGV	SIGLGKVLVD	1850
ILAGYGAGVA	GALVAFKMS	GEVPSTEDLV	NLLPAILSPG	ALVVGVCVAA	1900

FIG. 7G



10	20	30	40	50	
1234567890	1234567890	1234567890	1234567890	1234567890	
ILRRHVGPE	GAVQAMNRLI	AFASRGNHVS	PIHYVPESDA	AARVTQILSS	1950
LITITQLLKRL	HQWINEDCST	PCSGSWLRDV	WDWICTVLTD	FKTWLQSKLL	2000
PRLPGVPFLS	CQRGYKGVWR	GDGIMQITTCP	CGAQIAGHVK	NGSMRIVGPR	2050
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FIG. 7H



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Purcell, Robert

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Phe Arg Val Gly Trp Gly Ala Leu Gln Tyr Glu Asp Asn Val Thr Asn
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Pro Glu Asp Met Arg Pro Tyr Cys Trp His Tyr Pro Pro Arg Gln Cys
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Gly Val Val Ser Ala Lys Thr Val Cys Gly Pro Val Tyr Cys Phe Thr
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Pro Ser Pro Val Val Val Gly Thr Thr Asp Arg Leu Gly Ala Pro Thr
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Tyr Thr Trp Gly Glu Asn Glu Thr Asp Val Phe Leu Leu Asn Ser Thr
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Arg Pro Pro Leu Gly Ser Trp Phe Gly Cys Thr Trp Met Asn Ser Ser
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Gly Tyr Thr Lys Thr Cys Gly Ala Pro Pro Cys Arg Thr Arg Ala Asp
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Phe Asn Ala Ser Thr Asp Leu Leu Cys Pro Thr Asp Cys Phe Arg Lys
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His Pro Asp Thr Thr Tyr Leu Lys Cys Gly Ser Gly Pro Trp Leu Thr
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Pro Arg Cys Leu Ile Asp Tyr Pro Tyr Arg Leu Trp His Tyr Pro Cys
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Thr Val Asn Tyr Thr Ile Phe Lys Ile Arg Met Tyr Val Gly Gly Val
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Glu His Arg Leu Thr Ala Ala Cys Asn Phe Thr Arg Gly Asp Arg Cys
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Asn Leu Glu Asp Arg Asp Arg Ser Gln Leu Ser Pro Leu Leu His Ser
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Thr Thr Glu Trp Ala Ile Leu Pro Cys Ser Tyr Ser Asp Leu Pro Ala
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Leu Ser Thr Gly Leu Leu His Leu His Gln Asn Ile Val Asp Val Gln
690 695 700

Phe Met Tyr Gly Leu Ser Pro Ala Leu Thr Lys Tyr Ile Val Arg Trp
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Glu Trp Val Ile Leu Leu Phe Leu Leu Leu Ala Asp Ala Arg Val Cys
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Ala Cys Leu Trp Met Leu Ile Leu Leu Gly Gln Ala Glu Ala Ala Leu
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Glu Lys Leu Val Ile Leu His Ala Ala Ser Ala Ala Ser Cys Asn Gly
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Ala Pro Pro Met Gln Val Arg Gly Gly Arg Asp Gly Ile Ile Trp Ala
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Pro Ile Ile Phe Ser Pro Met Glu Lys Lys Val Ile Val Trp Gly Ala
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Glu Thr Ala Ala Cys Gly Asp Ile Leu His Gly Leu Pro Val Ser Ala
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Ser Met Met Ala Phe Ser Ala Ala Leu Thr Ser Pro Leu Ser Thr Ser		
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Thr Glu Asp Cys Pro Ile Pro Cys Gly Gly Ser Trp Leu Arg Asp Val		
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Trp Asp Trp Val Cys Thr Ile Leu Thr Asp Phe Lys Asn Trp Leu Thr		
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Ser Lys Leu Phe Pro Lys Met Pro Gly Leu Pro Phe Val Ser Cys Gln		
2005	2010	2015



Lys Gly Tyr Lys Gly Val Trp Ala Gly Thr Gly Ile Met Thr Thr Arg
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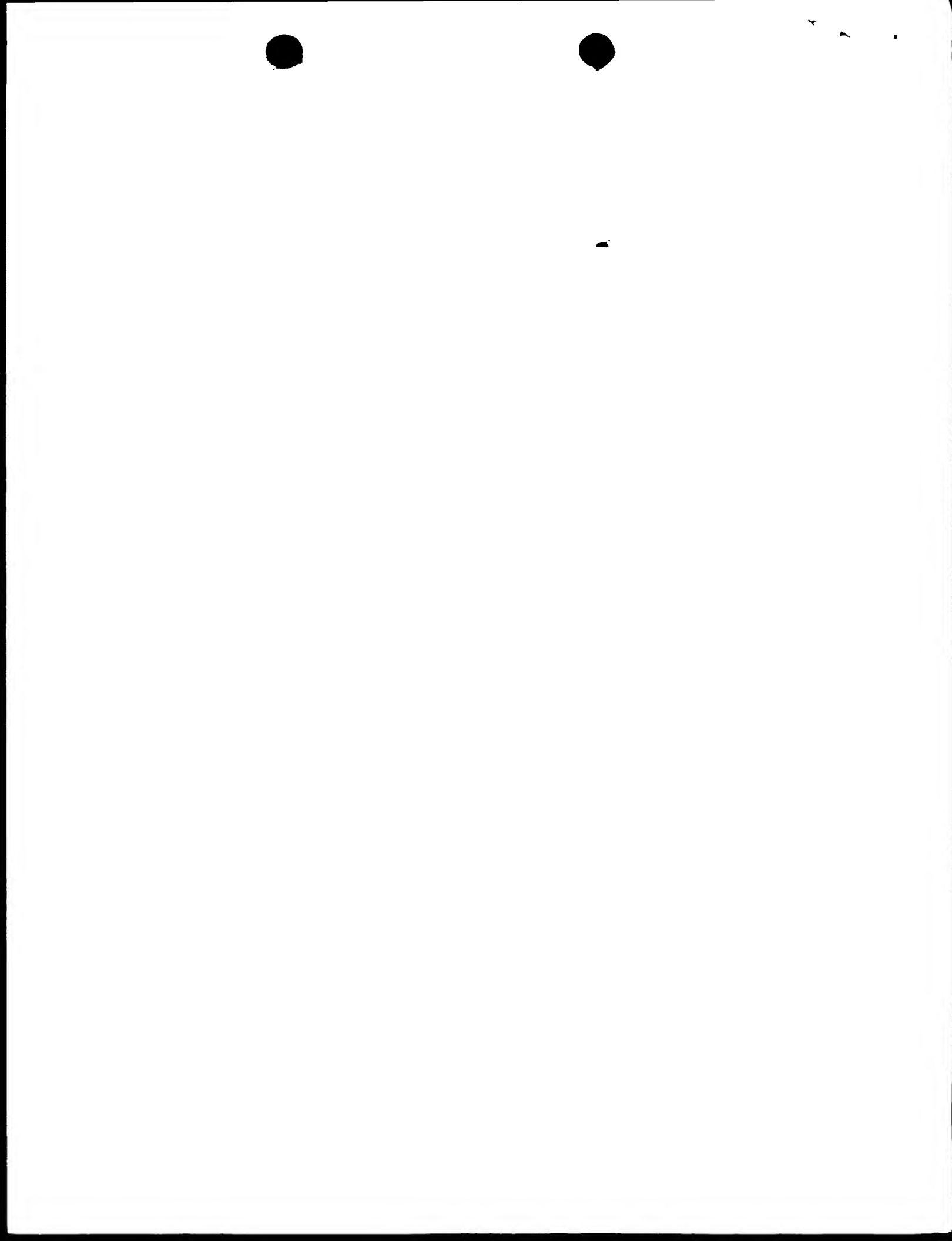
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<213> Hepatitis C virus

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1

2


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<211> 3015

<212> PRT

<213> Hepatitis C virus

<400> 4

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```

```

Arg Arg Pro Gln Asp Val Lys Phe Pro Gly Gly Gly Gln Ile Val Gly
      20              25              30

```

```

Gly Val Tyr Leu Leu Pro Arg Arg Gly Pro Arg Leu Gly Val Arg Ala
      35              40              45

```

```

Thr Arg Lys Thr Ser Glu Arg Ser Gln Pro Arg Gly Arg Arg Gln Pro
      50              55              60

```

```

Ile Pro Lys Asp Arg Arg Ser Thr Gly Lys Ser Trp Gly Lys Pro Gly
      65              70              75              80

```

```

Tyr Pro Trp Pro Leu Tyr Gly Asn Glu Gly Leu Gly Trp Ala Gly Trp

```



85

90

95

Leu Leu Ser Pro Arg Gly Ser Arg Pro Ser Trp Gly Pro Asn Asp Pro
 100 105 110

Arg His Arg Ser Arg Asn Val Gly Lys Val Ile Asp Thr Leu Thr Cys
 115 120 125

Gly Phe Ala Asp Leu Met Gly Tyr Ile Pro Val Val Gly Ala Pro Leu
 130 135 140

Gly Gly Val Ala Arg Ala Leu Ala His Gly Val Arg Val Leu Glu Asp
 145 150 155 160

Gly Val Asn Phe Ala Thr Gly Asn Leu Pro Gly Cys Ser Phe Ser Ile
 165 170 175

Phe Leu Leu Ala Leu Leu Ser Cys Ile Thr Thr Pro Val Ser Ala Ala
 180 185 190

Glu Val Lys Asn Ile Ser Thr Gly Tyr Met Val Thr Asn Asp Cys Thr
 195 200 205

Asn Asp Ser Ile Thr Trp Gln Leu Gln Ala Ala Val Leu His Val Pro
 210 215 220

Gly Cys Val Pro Cys Glu Lys Val Gly Asn Ala Ser Gln Cys Trp Ile
 225 230 235 240

Pro Val Ser Pro Asn Val Ala Val Gln Arg Pro Gly Ala Leu Thr Gln
 245 250 255

Gly Leu Arg Thr His Ile Asp Met Val Val Met Ser Ala Thr Leu Cys
 260 265 270

Ser Ala Leu Tyr Val Gly Asp Leu Cys Gly Gly Val Met Leu Ala Ala
 275 280 285

Gln Met Phe Ile Val Ser Pro Gln His His Trp Phe Val Gln Asp Cys
 290 295 300

Asn Cys Ser Ile Tyr Pro Gly Thr Ile Thr Gly His Arg Met Ala Trp
 305 310 315 320

Asp Met Met Met Asn Trp Ser Pro Thr Ala Thr Met Ile Leu Ala Tyr
 325 330 335

Ala Met Arg Val Pro Glu Val Ile Ile Asp Ile Ile Ser Gly Ala His



340	345	350
Trp Gly Val Met Phe Gly Leu Ala Tyr Phe Ser Met Gln Gly Ala Trp		
355	360	365
Ala Lys Val Val Val Ile Leu Leu Leu Ala Ala Gly Val Asp Ala Arg		
370	375	380
Thr His Thr Val Gly Gly Ser Ala Ala Gln Thr Thr Gly Arg Leu Thr		
385	390	395 400
Ser Leu Phe Asp Met Gly Pro Arg Gln Lys Ile Gln Leu Val Asn Thr		
405	410	415
Asn Gly Ser Trp His Ile Asn Arg Thr Ala Leu Asn Cys Asn Asp Ser		
420	425	430
Leu His Thr Gly Phe Ile Ala Ser Leu Phe Tyr Thr His Ser Phe Asn		
435	440	445
Ser Ser Gly Cys Pro Glu Arg Met Ser Ala Cys Arg Ser Ile Glu Ala		
450	455	460
Phe Arg Val Gly Trp Gly Ala Leu Gln Tyr Glu Asp Asn Val Thr Asn		
465	470	475 480
Pro Glu Asp Met Arg Pro Tyr Cys Trp His Tyr Pro Pro Arg Gln Cys		
485	490	495
Gly Val Val Ser Ala Lys Thr Val Cys Gly Pro Val Tyr Cys Phe Thr		
500	505	510
Pro Ser Pro Val Val Val Gly Thr Thr Asp Arg Leu Gly Ala Pro Thr		
515	520	525
Tyr Thr Trp Gly Glu Asn Glu Thr Asp Val Phe Leu Leu Asn Ser Thr		
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Arg Pro Pro Leu Gly Ser Trp Phe Gly Cys Thr Trp Met Asn Ser Ser		
545	550	555 560
Gly Tyr Thr Lys Thr Cys Gly Ala Pro Pro Cys Arg Thr Arg Ala Asp		
565	570	575
Phe Asn Ala Ser Thr Asp Leu Leu Cys Pro Thr Asp Cys Phe Arg Lys		
580	585	590
His Pro Asp Thr Thr Tyr Leu Lys Cys Gly Ser Gly Pro Trp Leu Thr		



595

600

605

Pro Arg Cys Leu Ile Asp Tyr Pro Tyr Arg Leu Trp His Tyr Pro Cys
 610 615 620

Thr Val Asn Tyr Thr Ile Phe Lys Ile Arg Met Tyr Val Gly Gly Val
 625 630 635 640

Glu His Arg Leu Thr Ala Ala Cys Asn Phe Thr Arg Gly Asp Arg Cys
 645 650 655

Asn Leu Glu Asp Arg Asp Arg Ser Gln Leu Ser Pro Leu Leu His Ser
 660 665 670

Thr Thr Glu Trp Ala Ile Leu Pro Cys Ser Tyr Ser Asp Leu Pro Ala
 675 680 685

Leu Ser Thr Gly Leu Leu His Leu His Gln Asn Ile Val Asp Val Gln
 690 695 700

Phe Met Tyr Gly Leu Ser Pro Ala Leu Thr Lys Tyr Ile Val Arg Trp
 705 710 715 720

Glu Trp Val Ile Leu Leu Phe Leu Leu Leu Ala Asp Ala Arg Val Cys
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Ala Cys Leu Trp Met Leu Ile Leu Leu Gly Gln Ala Glu Ala Ala Leu
 740 745 750

Glu Lys Leu Val Ile Leu His Ala Ala Ser Ala Ala Ser Cys Asn Gly
 755 760 765

Phe Leu Tyr Phe Val Ile Phe Phe Val Ala Ala Trp Tyr Ile Lys Gly
 770 775 780

Arg Val Val Pro Leu Ala Thr Tyr Ser Leu Thr Gly Leu Trp Ser Phe
 785 790 795 800

Ser Leu Leu Leu Leu Ala Leu Pro Gln Gln Ala Tyr Ala Leu Asp Thr
 805 810 815

Glu Val Ala Ala Ser Cys Gly Gly Val Val Leu Val Gly Leu Met Ala
 820 825 830

Leu Thr Leu Ser Pro Tyr Tyr Lys Arg Tyr Ile Ser Trp Cys Met Trp
 835 840 845

Trp Leu Gln Tyr Phe Leu Thr Arg Val Glu Ala Gln Leu His Val Trp



850	855	860
Val Pro Pro Leu Asn Val Arg Gly Gly Arg Asp Ala Val Ile Leu Leu		
865	870	875 880
Met Cys Val Val His Pro Thr Leu Val Phe Asp Ile Thr Lys Leu Leu		
	885	890 895
Leu Ala Ile Phe Gly Pro Leu Trp Ile Leu Gln Ala Ser Leu Leu Lys		
	900	905 910
Val Pro Tyr Phe Val Arg Val Gln Gly Leu Leu Arg Ile Cys Ala Leu		
	915	920 925
Ala Arg Lys Ile Ala Gly Gly His Tyr Val Gln Met Ala Ile Ile Lys		
	930	935 940
Leu Gly Ala Leu Thr Gly Thr Tyr Val Tyr Asn His Leu Thr Pro Leu		
	945	950 955 960
Arg Asp Trp Ala His Asn Gly Leu Arg Asp Leu Ala Val Ala Val Glu		
	965	970 975
Pro Val Val Phe Ser Arg Met Glu Thr Lys Leu Ile Thr Trp Gly Ala		
	980	985 990
Asp Thr Ala Ala Cys Gly Asp Ile Ile Asn Gly Leu Pro Val Ser Ala		
	995	1000 1005
Arg Arg Gly Gln Glu Ile Leu Leu Gly Pro Ala Asp Gly Met Val Ser		
	1010	1015 1020
Lys Gly Trp Arg Leu Leu Ala Pro Ile Thr Ala Tyr Ala Gln Gln Thr		
	1025	1030 1035 1040
Arg Gly Leu Leu Gly Cys Ile Ile Thr Ser Leu Thr Gly Arg Asp Lys		
	1045	1050 1055
Asn Gln Val Glu Gly Glu Val Gln Ile Val Ser Thr Ala Thr Gln Thr		
	1060	1065 1070
Phe Leu Ala Thr Cys Ile Asn Gly Val Cys Trp Thr Val Tyr His Gly		
	1075	1080 1085
Ala Gly Thr Arg Thr Ile Ala Ser Pro Lys Gly Pro Val Ile Gln Met		
	1090	1095 1100
Tyr Thr Asn Val Asp Gln Asp Leu Val Gly Trp Pro Ala Pro Gln Gly		



1105	1110	1115	1120
Ser Arg Ser Leu Thr Pro Cys Thr Cys Gly Ser Ser Asp Leu Tyr Leu			
1125	1130	1135	
Val Thr Arg His Ala Asp Val Ile Pro Val Arg Arg Arg Gly Asp Ser			
1140	1145	1150	
Arg Gly Ser Leu Leu Ser Pro Arg Pro Ile Ser Tyr Leu Lys Gly Ser			
1155	1160	1165	
Ser Gly Gly Pro Leu Leu Cys Pro Ala Gly His Ala Val Gly Leu Phe			
1170	1175	1180	
Arg Ala Ala Val Cys Thr Arg Gly Val Ala Lys Ala Val Asp Phe Ile			
1185	1190	1195	1200
Pro Val Glu Asn Leu Gly Thr Thr Met Arg Ser Pro Val Phe Thr Asp			
1205	1210	1215	
Asn Ser Ser Pro Pro Ala Val Pro Gln Ser Phe Gln Val Ala His Leu			
1220	1225	1230	
His Ala Pro Thr Gly Ser Gly Lys Ser Thr Lys Val Pro Ala Ala Tyr			
1235	1240	1245	
Ala Ala Gln Gly Tyr Lys Val Leu Val Leu Asn Pro Ser Val Ala Ala			
1250	1255	1260	
Thr Leu Gly Phe Gly Ala Tyr Met Ser Lys Ala His Gly Val Asp Pro			
1265	1270	1275	1280
Asn Ile Arg Thr Gly Val Arg Thr Ile Thr Thr Gly Ser Pro Ile Thr			
1285	1290	1295	
Tyr Ser Thr Tyr Gly Lys Phe Leu Ala Asp Gly Gly Cys Ser Gly Gly			
1300	1305	1310	
Ala Tyr Asp Ile Ile Ile Cys Asp Glu Cys His Ser Thr Asp Ala Thr			
1315	1320	1325	
Ser Ile Leu Gly Ile Gly Thr Val Leu Asp Gln Ala Glu Thr Ala Gly			
1330	1335	1340	
Ala Arg Leu Val Val Leu Ala Thr Ala Thr Pro Pro Gly Ser Val Thr			
1345	1350	1355	1360
Val Ser His Pro Asn Ile Glu Glu Val Ala Leu Ser Thr Thr Gly Glu			



1365	1370	1375
Ile Pro Phe Tyr Gly Lys Ala	Ile Pro Leu Glu Val	Ile Lys Gly Gly
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Arg His Leu Ile Phe Cys His Ser Lys Lys Lys Cys Asp Glu Leu Ala		
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Ala Lys Leu Val Ala Leu Gly Ile Asn Ala Val Ala Tyr Tyr Arg Gly		
1410	1415	1420
Leu Asp Val Ser Val Ile Pro Thr Ser Gly Asp Val Val Val Val Ser		
1425	1430	1435 1440
Thr Asp Ala Leu Met Thr Gly Phe Thr Gly Asp Phe Asp Ser Val Ile		
1445	1450	1455
Asp Cys Asn Thr Cys Val Thr Gln Thr Val Asp Phe Ser Leu Asp Pro		
1460	1465	1470
Thr Phe Thr Ile Glu Thr Thr Thr Leu Pro Gln Asp Ala Val Ser Arg		
1475	1480	1485
Thr Gln Arg Arg Gly Arg Thr Gly Arg Gly Lys Pro Gly Ile Tyr Arg		
1490	1495	1500
Phe Val Ala Pro Gly Glu Arg Pro Ser Gly Met Phe Asp Ser Ser Val		
1505	1510	1515 1520
Leu Cys Glu Cys Tyr Asp Ala Gly Cys Ala Trp Tyr Glu Leu Thr Pro		
1525	1530	1535
Ala Glu Thr Thr Val Arg Leu Arg Ala Tyr Met Asn Thr Pro Gly Leu		
1540	1545	1550
Pro Val Cys Gln Asp His Leu Glu Phe Trp Glu Gly Val Phe Thr Gly		
1555	1560	1565
Leu Thr His Ile Asp Ala His Phe Leu Ser Gln Thr Lys Gln Ser Gly		
1570	1575	1580
Glu Asn Phe Pro Tyr Leu Val Ala Tyr Gln Ala Thr Val Cys Ala Arg		
1585	1590	1595 1600
Ala Gln Ala Pro Pro Pro Ser Trp Asp Gln Met Trp Lys Cys Leu Ile		
1605	1610	1615
Arg Leu Lys Pro Thr Leu His Gly Pro Thr Pro Leu Leu Tyr Arg Leu		



1620	1625	1630
Gly Ala Val Gln Asn Glu Val Thr Leu Thr His Pro Ile Thr Lys Tyr		
1635	1640	1645
Ile Met Thr Cys Met Ser Ala Asp Leu Glu Val Val Thr Ser Thr Trp		
1650	1655	1660
Val Leu Val Gly Gly Val Leu Ala Ala Leu Ala Ala Tyr Cys Leu Ser		
1665	1670	1675 1680
Thr Gly Cys Val Val Ile Val Gly Arg Ile Val Leu Ser Gly Lys Pro		
1685	1690	1695
Ala Ile Ile Pro Asp Arg Glu Val Leu Tyr Gln Glu Phe Asp Glu Met		
1700	1705	1710
Glu Glu Cys Ser Gln His Leu Pro Tyr Ile Glu Gln Gly Met Met Leu		
1715	1720	1725
Ala Glu Gln Phe Lys Gln Lys Ala Leu Gly Leu Leu Gln Thr Ala Ser		
1730	1735	1740
Arg His Ala Glu Val Ile Thr Pro Ala Val Gln Thr Asn Trp Gln Lys		
1745	1750	1755 1760
Leu Glu Val Phe Trp Ala Lys His Met Trp Asn Phe Ile Ser Gly Ile		
1765	1770	1775
Gln Tyr Leu Ala Gly Leu Ser Thr Leu Pro Gly Asn Pro Ala Ile Ala		
1780	1785	1790
Ser Leu Met Ala Phe Thr Ala Ala Val Thr Ser Pro Leu Thr Thr Gly		
1795	1800	1805
Gln Thr Leu Leu Phe Asn Ile Leu Gly Gly Trp Val Ala Ala Gln Leu		
1810	1815	1820
Ala Ala Pro Gly Ala Ala Thr Ala Phe Val Gly Ala Gly Leu Ala Gly		
1825	1830	1835 1840
Ala Ala Ile Gly Ser Val Gly Leu Gly Lys Val Leu Val Asp Ile Leu		
1845	1850	1855
Ala Gly Tyr Gly Ala Gly Val Ala Gly Ala Leu Val Ala Phe Lys Ile		
1860	1865	1870
Met Ser Gly Glu Val Pro Ser Thr Glu Asp Leu Val Asn Leu Leu Pro		



1875	1880	1885
Ala Ile Leu Ser Pro Gly Ala Leu Val Val Gly Val Val Cys Ala Ala		
1890	1895	1900
Ile Leu Arg Arg His Val Gly Pro Gly Glu Gly Ala Val Gln Trp Met		
1905	1910	1915 1920
Asn Arg Leu Ile Ala Phe Ala Ser Arg Gly Asn His Val Ser Pro Thr		
1925	1930	1935
His Tyr Val Pro Glu Ser Asp Ala Ala Ala Arg Val Thr Ala Ile Leu		
1940	1945	1950
Ser Ser Leu Thr Val Thr Gln Leu Leu Arg Arg Leu His Gln Trp Ile		
1955	1960	1965
Ser Ser Glu Cys Thr Thr Pro Cys Ser Gly Ser Trp Leu Arg Asp Ile		
1970	1975	1980
Trp Asp Trp Ile Cys Glu Val Leu Ser Asp Phe Lys Thr Trp Leu Lys		
1985	1990	1995 2000
Ala Lys Leu Met Pro Gln Leu Pro Gly Ile Pro Phe Val Ser Cys Gln		
2005	2010	2015
Arg Gly Tyr Arg Gly Val Trp Arg Gly Asp Gly Ile Met His Thr Arg		
2020	2025	2030
Cys His Cys Gly Ala Glu Ile Thr Gly His Val Lys Asn Gly Thr Met		
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Arg Ile Val Gly Pro Arg Thr Cys Arg Asn Met Trp Ser Gly Thr Phe		
2050	2055	2060
Pro Ile Asn Ala Tyr Thr Thr Gly Pro Cys Thr Pro Leu Pro Ala Pro		
2065	2070	2075 2080
Asn Tyr Lys Phe Ala Leu Trp Arg Val Ser Ala Glu Glu Tyr Val Glu		
2085	2090	2095
Ile Arg Arg Val Gly Asp Phe His Tyr Val Ser Gly Met Thr Thr Asp		
2100	2105	2110
Asn Leu Lys Cys Pro Cys Gln Ile Pro Ser Pro Glu Phe Phe Thr Glu		
2115	2120	2125
Leu Asp Gly Val Arg Leu His Arg Phe Ala Pro Pro Cys Lys Pro Leu		



2130	2135	2140
Leu Arg Glu Glu Val Ser Phe Arg Val Gly Leu His Glu Tyr Pro Val		
2145	2150	2155 2160
Gly Ser Gln Leu Pro Cys Glu Pro Glu Pro Asp Val Ala Val Leu Thr		
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Ser Met Leu Thr Asp Pro Ser His Ile Thr Ala Glu Ala Ala Gly Arg		
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Arg Leu Ala Arg Gly Ser Pro Pro Ser Met Ala Ser Ser Ser Ala Ser		
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Gln Leu Ser Ala Pro Ser Leu Lys Ala Thr Cys Thr Ala Asn His Asp		
2210	2215	2220
Ser Pro Asp Ala Glu Leu Ile Glu Ala Asn Leu Leu Trp Arg Gln Glu		
2225	2230	2235 2240
Met Gly Gly Asn Ile Thr Arg Val Glu Ser Glu Asn Lys Val Val Ile		
2245	2250	2255
Leu Asp Ser Phe Asp Pro Leu Val Ala Glu Glu Asp Glu Arg Glu Val		
2260	2265	2270
Ser Val Pro Ala Glu Ile Leu Arg Lys Ser Arg Arg Phe Ala Arg Ala		
2275	2280	2285
Leu Pro Val Trp Ala Arg Pro Asp Tyr Asn Pro Pro Leu Val Glu Thr		
2290	2295	2300
Trp Lys Lys Pro Asp Tyr Glu Pro Pro Val Val His Gly Cys Pro Leu		
2305	2310	2315 2320
Pro Pro Pro Arg Ser Pro Pro Val Pro Pro Pro Arg Lys Lys Arg Thr		
2325	2330	2335
Val Val Leu Thr Glu Ser Thr Leu Ser Thr Ala Leu Ala Glu Leu Ala		
2340	2345	2350
Thr Lys Ser Phe Gly Ser Ser Ser Thr Ser Gly Ile Thr Gly Asp Asn		
2355	2360	2365
Thr Thr Thr Ser Ser Glu Pro Ala Pro Ser Gly Cys Pro Pro Asp Ser		
2370	2375	2380
Asp Val Glu Ser Tyr Ser Ser Met Pro Pro Leu Glu Gly Glu Pro Gly		



2385	2390	2395	2400
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2405	2410	2415	
Asp Thr Glu Asp Val Val Cys Cys Ser Met Ser Tyr Ser Trp Thr Gly			
2420	2425	2430	
Ala Leu Val Thr Pro Cys Ala Ala Glu Glu Gln Lys Leu Pro Ile Asn			
2435	2440	2445	
Ala Leu Ser Asn Ser Leu Leu Arg His His Asn Leu Val Tyr Ser Thr			
2450	2455	2460	
Thr Ser Arg Ser Ala Cys Gln Arg Gln Lys Lys Val Thr Phe Asp Arg			
2465	2470	2475	2480
Leu Gln Val Leu Asp Ser His Tyr Gln Asp Val Leu Lys Glu Val Lys			
2485	2490	2495	
Ala Ala Ala Ser Lys Val Lys Ala Asn Leu Leu Ser Val Glu Glu Ala			
2500	2505	2510	
Cys Ser Leu Thr Pro Pro His Ser Ala Lys Ser Lys Phe Gly Tyr Gly			
2515	2520	2525	
Ala Lys Asp Val Arg Cys His Ala Arg Lys Ala Val Ala His Ile Asn			
2530	2535	2540	
Ser Val Trp Lys Asp Leu Leu Glu Asp Ser Val Thr Pro Ile Asp Thr			
2545	2550	2555	2560
Thr Ile Met Ala Lys Asn Glu Val Phe Cys Val Gln Pro Glu Lys Gly			
2565	2570	2575	
Gly Arg Lys Pro Ala Arg Leu Ile Val Phe Pro Asp Leu Gly Val Arg			
2580	2585	2590	
Val Cys Glu Lys Met Ala Leu Tyr Asp Val Val Ser Lys Leu Pro Leu			
2595	2600	2605	
Ala Val Met Gly Ser Ser Tyr Gly Phe Gln Tyr Ser Pro Gly Gln Arg			
2610	2615	2620	
Val Glu Phe Leu Val Gln Ala Trp Lys Ser Lys Lys Thr Pro Met Gly			
2625	2630	2635	2640
Phe Ser Tyr Asp Thr Arg Cys Phe Asp Ser Thr Val Thr Glu Ser Asp			



2645	2650	2655
Ile Arg Thr Glu Glu Ala Ile Tyr Gln Cys Cys Asp Leu Asp Pro Gln		
2660	2665	2670
Ala Arg Val Ala Ile Lys Ser Leu Thr Glu Arg Leu Tyr Val Gly Gly		
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<212> PRT

<213> Hepatitis C virus

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Leu Leu Ser Pro Arg Gly Ser Arg Pro Ser Trp Gly Pro Asn Asp Pro
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Glu	Trp	Val	Ile	Leu	Leu	Phe	Leu	Leu	Leu	Ala	Asp	Ala	Arg	Val	Cys	725	730	735



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Leu Val Ser Phe Leu Val Phe Phe Cys Phe Ala Trp Tyr Leu Lys Gly	770	775	780
Arg Trp Val Pro Gly Ala Val Tyr Ala Leu Tyr Gly Met Trp Pro Leu	785	790	795
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Met Cys Val Val His Pro Thr Leu Val Phe Asp Ile Thr Lys Leu Leu	885	890	895
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Val Pro Tyr Phe Val Arg Val Gln Gly Leu Leu Arg Ile Cys Ala Leu	915	920	925
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Ile Pro Lys Asp Arg Arg Ser Thr Gly Lys Ser Trp Gly Lys Pro Gly
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Tyr Pro Trp Pro Leu Tyr Gly Asn Glu Gly Leu Gly Trp Ala Gly Trp
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Leu Leu Ser Pro Arg Gly Ser Arg Pro Ser Trp Gly Pro Asn Asp Pro
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Arg His Arg Ser Arg Asn Val Gly Lys Val Ile Asp Thr Leu Thr Cys
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Gly Phe Ala Asp Leu Met Gly Tyr Ile Pro Val Val Gly Ala Pro Leu
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Gly Gly Val Ala Arg Ala Leu Ala His Gly Val Arg Val Leu Glu Asp
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Gly Val Asn Phe Ala Thr Gly Asn Leu Pro Gly Cys Ser Phe Ser Ile
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Phe Leu Leu Ala Leu Leu Ser Cys Ile Thr Thr Pro Val Ser Ala Ala
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Glu Val Lys Asn Ile Ser Thr Gly Tyr Met Val Thr Asn Asp Cys Thr
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Asn Asp Ser Ile Thr Trp Gln Leu Gln Ala Ala Val Leu His Val Pro
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Gly Cys Val Pro Cys Glu Lys Val Gly Asn Ala Ser Gln Cys Trp Ile
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Pro Val Ser Pro Asn Val Ala Val Gln Arg Pro Gly Ala Leu Thr Gln
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Ser Ala Leu Tyr Val Gly Asp Leu Cys Gly Gly Val Met Leu Ala Ala
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Gln Met Phe Ile Val Ser Pro Gln His His Trp Phe Val Gln Asp Cys
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Asp Met Met Met Asn Trp Ser Pro Thr Ala Thr Met Ile Leu Ala Tyr
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Ala Met Arg Val Pro Glu Val Ile Ile Asp Ile Ile Ser Gly Ala His
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Trp Gly Val Met Phe Gly Leu Ala Tyr Phe Ser Met Gln Gly Ala Trp
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Thr His Thr Val Gly Gly Ser Ala Ala Gln Thr Thr Gly Arg Leu Thr
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Pro Ser Pro Val Val Val Gly Thr Thr Asp Arg Leu Gly Ala Pro Thr
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Tyr Thr Trp Gly Glu Asn Glu Thr Asp Val Phe Leu Leu Asn Ser Thr
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Pro Arg Cys Leu Ile Asp Tyr Pro Tyr Arg Leu Trp His Tyr Pro Cys
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660 665 670

Thr Thr Glu Trp Ala Ile Leu Pro Cys Ser Tyr Ser Asp Leu Pro Ala
675 680 685

Leu Ser Thr Gly Leu Leu His Leu His Gln Asn Ile Val Asp Val Gln
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Phe Met Tyr Gly Leu Ser Pro Ala Leu Thr Lys Tyr Ile Val Arg Trp
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Glu Trp Val Ile Leu Leu Phe Leu Leu Leu Ala Asp Ala Arg Val Cys
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Ala Cys Leu Trp Met Leu Ile Leu Leu Gly Gln Ala Glu Ala Ala Leu
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Glu Lys Leu Val Ile Leu His Ala Ala Ser Ala Ala Ser Cys Asn Gly
755 760 765

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Ser Leu Leu Leu Leu Ala Leu Pro Gln Ala Tyr Ala Leu Asp Thr
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Met Cys Val Val His Pro Thr Leu Val Phe Asp Ile Thr Lys Leu Leu
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Val Pro Tyr Phe Val Arg Val Gln Gly Leu Leu Arg Ile Cys Ala Leu
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Asp Thr Ala Ala Cys Gly Asp Ile Ile Asn Gly Leu Pro Val Ser Ala
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Asn Ile Arg Thr Gly Val Arg Thr Ile Thr Thr Gly Ser Pro Ile Thr
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Tyr Ser Thr Tyr Gly Lys Phe Leu Ala Asp Gly Gly Cys Ser Gly Gly
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Ser Ile Leu Gly Ile Gly Thr Val Leu Asp Gln Ala Glu Thr Ala Gly
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Ala Arg Leu Val Val Leu Ala Thr Ala Thr Pro Pro Gly Ser Val Thr
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Val Ser His Pro Asn Ile Glu Glu Val Ala Leu Ser Thr Thr Gly Glu
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Ile Pro Phe Tyr Gly Lys Ala Ile Pro Leu Glu Val Ile Lys Gly Gly
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Arg His Leu Ile Phe Cys His Ser Lys Lys Lys Cys Asp Glu Leu Ala
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Val Leu Val Gly Gly Val Leu Ala Ala Leu Ala Ala Tyr Cys Leu Ser
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Thr Gly Cys Val Val Ile Val Gly Arg Ile Val Leu Ser Gly Lys Pro
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Gln Tyr Leu Ala Gly Leu Ser Thr Leu Pro Gly Asn Pro Ala Ile Ala
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Ser Leu Met Ala Phe Thr Ala Ala Val Thr Ser Pro Leu Thr Thr Gly
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Gln Thr Leu Leu Phe Asn Ile Leu Gly Gly Trp Val Ala Ala Gln Leu
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Ala Ala Pro Gly Ala Ala Thr Ala Phe Val Gly Ala Gly Leu Ala Gly
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Ala Ala Ile Gly Ser Val Gly Leu Gly Lys Val Leu Val Asp Ile Leu
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Ala Gly Tyr Gly Ala Gly Val Ala Gly Ala Leu Val Ala Phe Lys Ile
1860 1865 1870

Met Ser Gly Glu Val Pro Ser Thr Glu Asp Leu Val Asn Leu Leu Pro
1875 1880 1885



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<212> PRT

<213> Hepatitis C virus

<400> 10

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 35 40 45

Thr Arg Lys Thr Ser Glu Arg Ser Gln Pro Arg Gly Arg Arg Gln Pro
 50 55 60

Ile Pro Lys Asp Arg Arg Ser Thr Gly Lys Ser Trp Gly Lys Pro Gly
 65 70 75 80

Tyr Pro Trp Pro Leu Tyr Gly Asn Glu Gly Leu Gly Trp Ala Gly Trp
 85 90 95

Leu Leu Ser Pro Arg Gly Ser Arg Pro Ser Trp Gly Pro Asn Asp Pro
 100 105 110

Arg His Arg Ser Arg Asn Val Gly Lys Val Ile Asp Thr Leu Thr Cys
 115 120 125

Gly Phe Ala Asp Leu Met Gly Tyr Ile Pro Val Val Gly Ala Pro Leu
 130 135 140

Gly Gly Val Ala Arg Ala Leu Ala His Gly Val Arg Val Leu Glu Asp
 145 150 155 160

Gly Val Asn Phe Ala Thr Gly Asn Leu Pro Gly Cys Ser Phe Ser Ile
 165 170 175

Phe Leu Leu Ala Leu Leu Ser Cys Ile Thr Thr Pro Val Ser Ala Ala
 180 185 190

Glu Val Lys Asn Ile Ser Thr Gly Tyr Met Val Thr Asn Asp Cys Thr
 195 200 205

Asn Asp Ser Ile Thr Trp Gln Leu Gln Ala Ala Val Leu His Val Pro
 210 215 220

Gly Cys Val Pro Cys Glu Lys Val Gly Asn Ala Ser Gln Cys Trp Ile



225	230	235	240
Pro Val Ser Pro Asn Val Ala Val Gln Arg Pro Gly Ala Leu Thr Gln	245	250	255
Gly Leu Arg Thr His Ile Asp Met Val Val Met Ser Ala Thr Leu Cys	260	265	270
Ser Ala Leu Tyr Val Gly Asp Leu Cys Gly Gly Val Met Leu Ala Ala	275	280	285
Gln Met Phe Ile Val Ser Pro Gln His His Trp Phe Val Gln Asp Cys	290	295	300
Asn Cys Ser Ile Tyr Pro Gly Thr Ile Thr Gly His Arg Met Ala Trp	305	310	315
Asp Met Met Met Asn Trp Ser Pro Thr Ala Thr Met Ile Leu Ala Tyr	325	330	335
Ala Met Arg Val Pro Glu Val Ile Ile Asp Ile Ile Ser Gly Ala His	340	345	350
Trp Gly Val Met Phe Gly Leu Ala Tyr Phe Ser Met Gln Gly Ala Trp	355	360	365
Ala Lys Val Val Val Ile Leu Leu Leu Ala Ala Gly Val Asp Ala Arg	370	375	380
Thr His Thr Val Gly Gly Ser Ala Ala Gln Thr Thr Gly Arg Leu Thr	385	390	395
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Leu His Thr Gly Phe Ile Ala Ser Leu Phe Tyr Thr His Ser Phe Asn	435	440	445
Ser Ser Gly Cys Pro Glu Arg Met Ser Ala Cys Arg Ser Ile Glu Ala	450	455	460
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Thr Thr Glu Trp Ala Ile Leu Pro Cys Ser Tyr Ser Asp Leu Pro Ala 675	680	685
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Val Pro Tyr Phe Val Arg Val Gln Gly Leu Leu Arg Ile Cys Ala Leu		
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Ala Arg Lys Ile Ala Gly Gly His Tyr Val Gln Met Ala Ile Ile Lys		
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Asp Thr Ala Ala Cys Gly Asp Ile Ile Asn Gly Leu Pro Val Ser Ala		



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1570	1575	1580	
Glu Asn Phe Pro Tyr Leu Val Ala Tyr Gln Ala Thr Val Cys Ala Arg			
1585	1590	1595	1600
Ala Gln Ala Pro Pro Pro Ser Trp Asp Gln Met Trp Lys Cys Leu Ile			
1605	1610	1615	
Arg Leu Lys Pro Thr Leu His Gly Pro Thr Pro Leu Leu Tyr Arg Leu			
1620	1625	1630	
Gly Ala Val Gln Asn Glu Val Thr Leu Thr His Pro Ile Thr Lys Tyr			
1635	1640	1645	
Ile Met Thr Cys Met Ser Ala Asp Leu Glu Val Val Thr Ser Thr Trp			
1650	1655	1660	
Val Leu Val Gly Gly Val Leu Ala Ala Leu Ala Ala Tyr Cys Leu Ser			
1665	1670	1675	1680
Thr Gly Cys Val Val Ile Val Gly Arg Ile Val Leu Ser Gly Lys Pro			
1685	1690	1695	
Ala Ile Ile Pro Asp Arg Glu Val Leu Tyr Gln Glu Phe Asp Glu Met			
1700	1705	1710	
Glu Glu Cys Ser Gln His Leu Pro Tyr Ile Glu Gln Gly Met Met Leu			
1715	1720	1725	
Ala Glu Gln Phe Lys Gln Lys Ala Leu Gly Leu Leu Gln Thr Ala Ser			
1730	1735	1740	
Arg His Ala Glu Val Ile Thr Pro Ala Val Gln Thr Asn Trp Gln Lys			
1745	1750	1755	1760
Leu Glu Val Phe Trp Ala Lys His Met Trp Asn Phe Ile Ser Gly Ile			



1765	1770	1775
Gln Tyr Leu Ala Gly Leu Ser Thr Leu Pro Gly Asn Pro Ala Ile Ala 1780	1785	1790
Ser Leu Met Ala Phe Thr Ala Ala Val Thr Ser Pro Leu Thr Thr Gly 1795	1800	1805
Gln Thr Leu Leu Phe Asn Ile Leu Gly Gly Trp Val Ala Ala Gln Leu 1810	1815	1820
Ala Ala Pro Gly Ala Ala Thr Ala Phe Val Gly Ala Gly Leu Ala Gly 1825	1830	1835 1840
Ala Ala Ile Gly Ser Val Gly Leu Gly Lys Val Leu Val Asp Ile Leu 1845	1850	1855
Ala Gly Tyr Gly Ala Gly Val Ala Gly Ala Leu Val Ala Phe Lys Ile 1860	1865	1870
Met Ser Gly Glu Val Pro Ser Thr Glu Asp Leu Val Asn Leu Leu Pro 1875	1880	1885
Ala Ile Leu Ser Pro Gly Ala Leu Val Val Gly Val Val Cys Ala Ala 1890	1895	1900
Ile Leu Arg Arg His Val Gly Pro Gly Glu Gly Ala Val Gln Trp Met 1905	1910	1915 1920
Asn Arg Leu Ile Ala Phe Ala Ser Arg Gly Asn His Val Ser Pro Thr 1925	1930	1935
His Tyr Val Pro Glu Ser Asp Ala Ala Ala Arg Val Thr Ala Ile Leu 1940	1945	1950
Ser Ser Leu Thr Val Thr Gln Leu Leu Arg Arg Leu His Gln Trp Ile 1955	1960	1965
Ser Ser Glu Cys Thr Thr Pro Cys Ser Gly Ser Trp Leu Arg Asp Ile 1970	1975	1980
Trp Asp Trp Ile Cys Glu Val Leu Ser Asp Phe Lys Thr Trp Leu Lys 1985	1990	1995 2000
Ala Lys Leu Met Pro Gln Leu Pro Gly Ile Pro Phe Val Ser Cys Gln 2005	2010	2015
Arg Gly Tyr Arg Gly Val Trp Arg Gly Asp Gly Ile Met His Thr Arg		



2020	2025	2030
Cys His Cys Gly Ala Glu Ile Thr Gly His Val Lys Asn Gly Thr Met 2035	2040	2045
Arg Ile Val Gly Pro Arg Thr Cys Arg Asn Met Trp Ser Gly Thr Phe 2050	2055	2060
Pro Ile Asn Ala Tyr Thr Thr Gly Pro Cys Thr Pro Leu Pro Ala Pro 2065	2070	2075 2080
Asn Tyr Lys Phe Ala Leu Trp Arg Val Ser Ala Glu Glu Tyr Val Glu 2085	2090	2095
Ile Arg Arg Val Gly Asp Phe His Tyr Val Ser Gly Met Thr Thr Asp 2100	2105	2110
Asn Leu Lys Cys Pro Cys Gln Ile Pro Ser Pro Glu Phe Phe Thr Glu 2115	2120	2125
Leu Asp Gly Val Arg Leu His Arg Phe Ala Pro Pro Cys Lys Pro Leu 2130	2135	2140
Leu Arg Glu Glu Val Ser Phe Arg Val Gly Leu His Glu Tyr Pro Val 2145	2150	2155 2160
Gly Ser Gln Leu Pro Cys Glu Pro Glu Pro Asp Val Ala Val Leu Thr 2165	2170	2175
Ser Met Leu Thr Asp Pro Ser His Ile Thr Ala Glu Ala Ala Gly Arg 2180	2185	2190
Arg Leu Ala Arg Gly Ser Pro Pro Ser Met Ala Ser Ser Ser Ala Ser 2195	2200	2205
Gln Leu Ser Ala Pro Ser Leu Lys Ala Thr Cys Thr Ala Asn His Asp 2210	2215	2220
Ser Pro Asp Ala Glu Leu Ile Glu Ala Asn Leu Leu Trp Arg Gln Glu 2225	2230	2235 2240
Met Gly Gly Asn Ile Thr Arg Val Glu Ser Glu Asn Lys Val Val Ile 2245	2250	2255
Leu Asp Ser Phe Asp Pro Leu Val Ala Glu Glu Asp Glu Arg Glu Val 2260	2265	2270
Ser Val Pro Ala Glu Ile Leu Arg Lys Ser Arg Arg Phe Ala Arg Ala		



2275	2280	2285
Leu Pro Val Trp Ala Arg Pro Asp Tyr Asn Pro Pro Leu Val Glu Thr		
2290	2295	2300
Trp Lys Lys Pro Asp Tyr Glu Pro Pro Val Val His Gly Cys Pro Leu		
2305	2310	2315 2320
Pro Pro Pro Arg Ser Pro Pro Val Pro Pro Pro Arg Lys Lys Arg Thr		
2325	2330	2335
Val Val Leu Thr Glu Ser Thr Leu Ser Thr Ala Leu Ala Glu Leu Ala		
2340	2345	2350
Thr Lys Ser Phe Gly Ser Ser Ser Thr Ser Gly Ile Thr Gly Asp Asn		
2355	2360	2365
Thr Thr Thr Ser Ser Glu Pro Ala Pro Ser Gly Cys Pro Pro Asp Ser		
2370	2375	2380
Asp Val Glu Ser Tyr Ser Ser Met Pro Pro Leu Glu Gly Glu Pro Gly		
2385	2390	2395 2400
Asp Pro Asp Leu Ser Asp Gly Ser Trp Ser Thr Val Ser Ser Gly Ala		
2405	2410	2415
Asp Thr Glu Asp Val Val Cys Cys Ser Met Ser Tyr Ser Trp Thr Gly		
2420	2425	2430
Ala Leu Val Thr Pro Cys Ala Ala Glu Glu Gln Lys Leu Pro Ile Asn		
2435	2440	2445
Ala Leu Ser Asn Ser Leu Leu Arg His His Asn Leu Val Tyr Ser Thr		
2450	2455	2460
Thr Ser Arg Ser Ala Cys Gln Arg Gln Lys Lys Val Thr Phe Asp Arg		
2465	2470	2475 2480
Leu Gln Val Leu Asp Ser His Tyr Gln Asp Val Leu Lys Glu Val Lys		
2485	2490	2495
Ala Ala Ala Ser Lys Val Lys Ala Asn Leu Leu Ser Val Glu Glu Ala		
2500	2505	2510
Cys Ser Leu Thr Pro Pro His Ser Ala Lys Ser Lys Phe Gly Tyr Gly		
2515	2520	2525
Ala Lys Asp Val Arg Cys His Ala Arg Lys Ala Val Ala His Ile Asn		



2530	2535	2540
Ser Val Trp Lys Asp Leu Leu Glu Asp Ser Val Thr Pro Ile Asp Thr		
2545	2550	2555 2560
Thr Ile Met Ala Lys Asn Glu Val Phe Cys Val Gln Pro Glu Lys Gly		
2565	2570	2575
Gly Arg Lys Pro Ala Arg Leu Ile Val Phe Pro Asp Leu Gly Val Arg		
2580	2585	2590
Val Cys Glu Lys Met Ala Leu Tyr Asp Val Val Ser Lys Leu Pro Leu		
2595	2600	2605
Ala Val Met Gly Ser Ser Tyr Gly Phe Gln Tyr Ser Pro Gly Gln Arg		
2610	2615	2620
Val Glu Phe Leu Val Gln Ala Trp Lys Ser Lys Lys Thr Pro Met Gly		
2625	2630	2635 2640
Phe Ser Tyr Asp Thr Arg Cys Phe Asp Ser Thr Val Thr Glu Ser Asp		
2645	2650	2655
Ile Arg Thr Glu Glu Ala Ile Tyr Gln Cys Cys Asp Leu Asp Pro Gln		
2660	2665	2670
Ala Arg Val Ala Ile Lys Ser Leu Thr Glu Arg Leu Tyr Val Gly Gly		
2675	2680	2685
Pro Leu Thr Asn Ser Arg Gly Glu Asn Cys Gly Tyr Arg Arg Cys Arg		
2690	2695	2700
Ala Ser Gly Val Leu Thr Thr Ser Cys Gly Asn Thr Leu Thr Cys Tyr		
2705	2710	2715 2720
Ile Lys Ala Arg Ala Ala Cys Arg Ala Ala Gly Leu Gln Asp Cys Thr		
2725	2730	2735
Met Leu Val Cys Gly Asp Asp Leu Val Val Ile Cys Glu Ser Ala Gly		
2740	2745	2750
Val Gln Glu Asp Ala Ala Ser Leu Arg Ala Phe Thr Glu Ala Met Thr		
2755	2760	2765
Arg Tyr Ser Ala Pro Pro Gly Asp Pro Pro Gln Pro Glu Tyr Asp Leu		
2770	2775	2780
Glu Leu Ile Thr Ser Cys Ser Ser Asn Val Ser Val Ala His Asp Gly		



2785 2790 2795 2800

Ala Gly Lys Arg Val Tyr Tyr Leu Thr Arg Asp Pro Thr Thr Pro Leu
 2805 2810 2815

Ala Arg Ala Ala Trp Glu Thr Ala Arg His Thr Pro Val Asn Ser Trp
 2820 2825 2830

Leu Gly Asn Ile Ile Met Phe Ala Pro Thr Leu Trp Ala Arg Met Ile
 2835 2840 2845

Leu Met Thr His Phe Phe Ser Val Leu Ile Ala Arg Asp Gln Leu Glu
 2850 2855 2860

Gln Ala Leu Asn Cys Glu Ile Tyr Gly Ala Cys Tyr Ser Ile Glu Pro
2865 2870 2875 2880

Leu Asp Leu Pro Pro Ile Ile Gln Arg Leu His Gly Leu Ser Ala Phe
 2885 2890 2895

Ser Leu His Ser Tyr Ser Pro Gly Glu Ile Asn Arg Val Ala Ala Cys
 2900 2905 2910

Leu Arg Lys Leu Gly Val Pro Pro Leu Arg Ala Trp Arg His Arg Ala
 2915 2920 2925

Arg Ser Val Arg Ala Arg Leu Leu Ser Arg Gly Gly Arg Ala Ala Ile
 2930 2935 2940

Cys Gly Lys Tyr Leu Phe Asn Trp Ala Val Arg Thr Lys Leu Lys Leu
2945 2950 2955 2960

Thr Pro Ile Ala Ala Ala Gly Arg Leu Asp Leu Ser Gly Trp Phe Thr
 2965 2970 2975

Ala Gly Tyr Ser Gly Gly Asp Ile Tyr His Ser Val Ser His Ala Arg
 2980 2985 2990

Pro Arg Trp Phe Trp Phe Cys Leu Leu Leu Leu Ala Ala Gly Val Gly
 2995 3000 3005

Ile Tyr Leu Leu Pro Asn Arg
 3010 3015

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<213> Hepatitis C virus

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24

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24

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<212> DNA

<213> Hepatitis C virus

<400> 13

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24

<210> 14

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<212> DNA

<213> Hepatitis C virus

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22

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<212> DNA

<213> Hepatitis C virus

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40

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24

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43



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26

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23

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<400> 30

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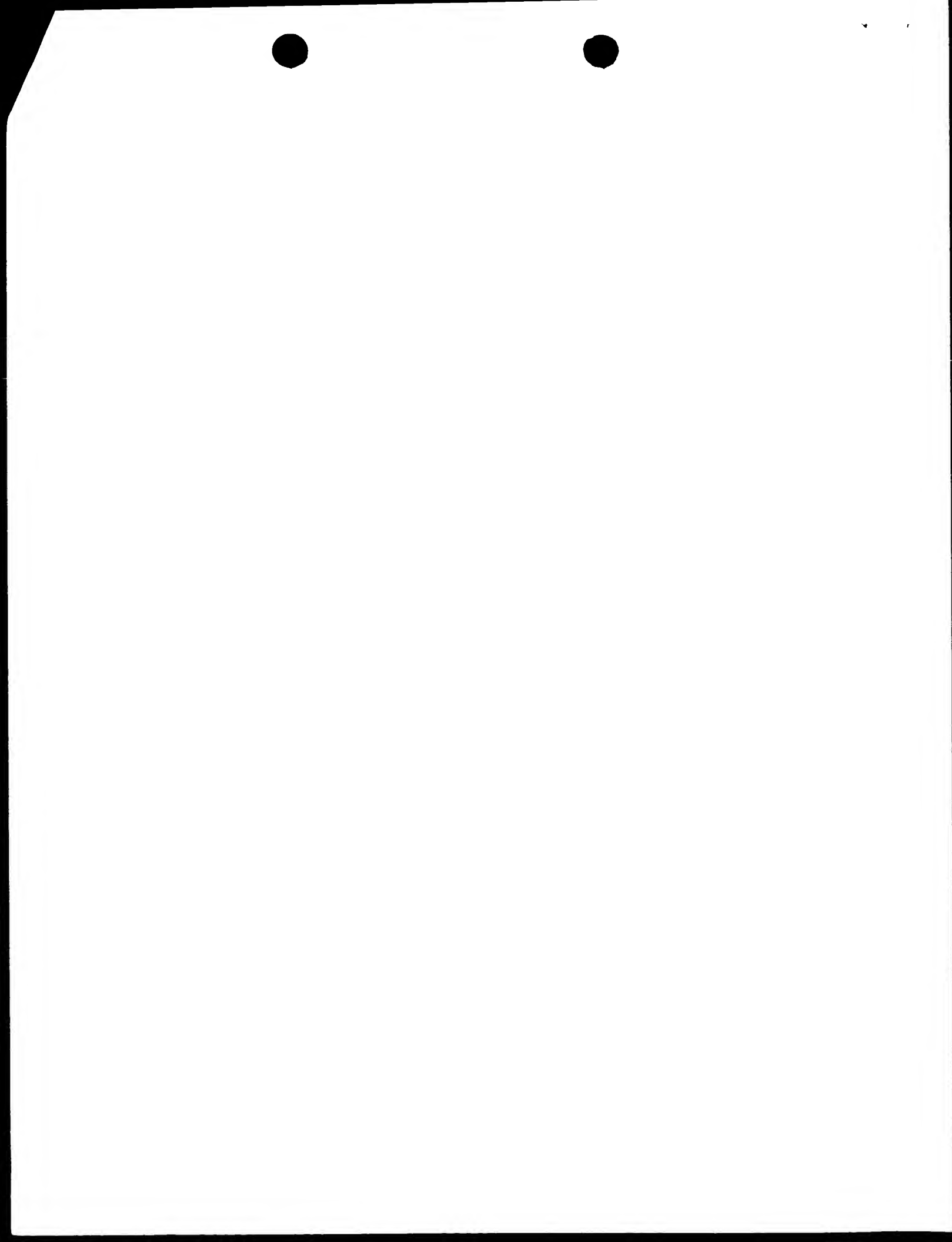
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24



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